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A 52-year-old woman comes to the emergency department due to recurrent right lower extremity swelling, pain, and erythema. The patient's medical history includes type 2 diabetes mellitus and depression. Her medications include metformin, paroxetine, and a multivitamin. The patient is diagnosed with cellulitis, admitted to the hospital, and started on antibiotics. She is continued on her home medications. Three days later, the patient becomes agitated and delirious with severe abdominal cramps and diarrhea. Her temperature is 39.2 C (102.6 F), blood pressure is 180/100 mm Hg, and heart rate is 120/min and regular. On examination, the patient is diaphoretic and tremulous, and her pupils are dilated. Bilateral hyperreflexia and ankle clonus are present. She begins to have seizures. Which of the following antibiotics was the patient most likely given to treat the cellulitis?

A. Clindamycin
B. Doxycycline
C. Linezolid
D. Penicillin
E. Vancomycin

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A 30-year-old woman comes to the office due to chronic anxiety and tension. The patient says she worries constantly about multiple issues involving her work, finances, and family. At work, she has difficulty concentrating as she repeatedly calls to check on the whereabouts and safety of her husband and children. The patient also describes frequent tension headaches, back pain, and fatigue. She does not feel depressed and says that her sleep and appetite are normal. Laboratory studies, including thyroid function tests, are within normal limits. In addition to a recommendation of psychotherapy, pharmacotherapy with buspirone is initiated. This medication is associated with which of the following properties?

- A. Antiseizure properties
- B. Efficacy in panic disorder
- C. Euphoric effects
- D. Muscle relaxant properties
- E. No risk of dependence
- F. Rapid onset of action

Submit

A 52-year-old woman comes to the emergency department due to recurrent right lower extremity swelling, pain, and erythema. The patient's medical history includes type 2 diabetes mellitus and depression. Her medications include metformin, paroxetine, and a multivitamin. The patient is diagnosed with cellulitis, admitted to the hospital, and started on antibiotics. She is continued on her home medications. Three days later, the patient becomes agitated and delirious with severe abdominal cramps and diarrhea. Her temperature is 39.2 C (102.6 F), blood pressure is 180/100 mm Hg, and heart rate is 120/min and regular. On examination, the patient is diaphoretic and tremulous, and her pupils are dilated. Bilateral hyperreflexia and ankle clonus are present. She begins to have seizures. Which of the following antibiotics was the patient most likely given to treat the cellulitis?

- A. Clindamycin (16%)
- B. Doxycycline (8%)
- ✓ C. Linezolid (58%)
- D. Penicillin (6%)
- E. Vancomycin (10%)

Omitted
Correct answer
C

58%
Answered correctly

03 secs
Time Spent

02/08/2020
Last Updated

Explanation

Serotonin syndrome	
	• Serotonergic medications, especially in combination (eg, SSRI/SNRI, TCA, tramadol)

A 52-year-old woman comes to the emergency department due to recurrent right lower extremity swelling, pain, and erythema. The patient's medical history includes type 2 diabetes mellitus and depression. Her medications include metformin, paroxetine, and a multivitamin. The patient is diagnosed with cellulitis, admitted to the hospital, and started on antibiotics. She is continued on her home medications. Three days later, the patient becomes agitated and delirious with severe abdominal cramps and diarrhea. Her temperature is 39.2 C (102.6 F), blood pressure is 180/100 mm Hg, and heart rate is 120/min and regular. On examination, the patient is diaphoretic and tremulous, and her pupils are dilated. Bilateral hyperreflexia and ankle clonus are present. She begins to have seizures. Which of the following antibiotics was the patient most likely given to treat the cellulitis?

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- B. Doxycycline (8%)
- ✓ C. Linezolid (58%)
- D. Penicillin (6%)
- E. Vancomycin (10%)

Omitted
Correct answer
C

58%
Answered correctly

03 secs
Time Spent

02/08/2020
Last Updated

Explanation

Serotonin syndrome	
	• Serotonergic medications, especially in combination (eg, SSRI/SNRI, TCA, tramadol)

Serotonin syndrome	
Causes	• Serotonergic medications, especially in combination (eg, SSRI/SNRI, TCA, tramadol) • Drug interactions: Serotonergic medication & MAOI or linezolid • Intentional overdose of serotonergic medications • Serotonergic drugs of abuse (eg, MDMA)
Clinical features	• Mental status changes (eg, anxiety, agitation, delirium) • Autonomic dysregulation (eg, diaphoresis, hypertension, tachycardia, hyperthermia, vomiting, diarrhea) • Neuromuscular hyperactivity (eg, tremor, myoclonus, hyperreflexia)

MAOI = monoamine oxidase inhibitor; **MDMA** = 3,4-Methylenedioxymethamphetamine;
SNRI = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant.

Serotonin syndrome is characterized by a triad of **autonomic instability** (eg, hyperthermia, hypertension, tachycardia), **altered mental status** (eg, agitation, confusion), and **neuromuscular hyperactivity** (eg, tremor, hyperreflexia, myoclonus), as well as gastrointestinal symptoms and diaphoresis. It is due to an increased serotonergic effect in the central nervous system (eg, increased 5-HT1A and 5-HT2A receptor stimulation).

Serotonin syndrome rarely occurs with a single serotonergic drug used at therapeutic doses. More commonly, it is due to the combined effects of several serotonergic medications, overdose, and/or a drug-drug interaction. Serotonin effect is increased when a **monoamine oxidase inhibitor** (MAOI) is **combined** with a **serotonergic antidepressant** (selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant).

Linezolid is used to treat infections caused by gram-positive bacteria, particularly vancomycin-resistant enterococcus and methicillin-resistant *Staphylococcus aureus*. **Linezolid has MAOI activity** and therefore can precipitate serotonin syndrome with concomitant use of an SSRI (eg, paroxetine) or with other serotonergic medications.

(Choices A, B, D, and E) Clindamycin, doxycycline, penicillin, and vancomycin do not have MAOI effects. They do not cause serotonin syndrome when combined with a serotonergic antidepressant.

Educational objective:

Serotonin syndrome is characterized by a triad of **autonomic instability** (eg, hyperthermia, hypertension, tachycardia), **altered mental status** (eg, agitation, confusion), and **neuromuscular hyperactivity** (eg, tremor, hyperreflexia, myoclonus), as well as gastrointestinal symptoms and diaphoresis. It is due to an increased serotonergic effect in the central nervous system (eg, increased 5-HT1A and 5-HT2A receptor stimulation).

Serotonin syndrome rarely occurs with a single serotonergic drug used at therapeutic doses. More commonly, it is due to the combined effects of several serotonergic medications, overdose, and/or a drug-drug interaction. Serotonin effect is increased when a **monoamine oxidase inhibitor** (MAOI) is **combined** with a **serotonergic antidepressant** (selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant).

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(Choices A, B, D, and E) Clindamycin, doxycycline, penicillin, and vancomycin do not have MAOI effects. They do not cause serotonin syndrome when combined with a serotonergic antidepressant.

Educational objective:
Serotonin syndrome is characterized by a triad of autonomic instability, altered mental status, and neuromuscular irritability. It may develop when a monoamine oxidase inhibitor (MAOI) antidepressant or a non-antidepressant with MAOI activity (eg, linezolid) is combined with a serotonergic medication such as a selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant.

References

- Clinical relevance of linezolid-associated serotonin toxicity.
- Serotonin syndrome due to co-administration of linezolid and methadone.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Serotonin syndrome
Subject	System	Topic

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A 30-year-old woman comes to the office due to chronic anxiety and tension. The patient says she worries constantly about multiple issues involving her work, finances, and family. At work, she has difficulty concentrating as she repeatedly calls to check on the whereabouts and safety of her husband and children. The patient also describes frequent tension headaches, back pain, and fatigue. She does not feel depressed and says that her sleep and appetite are normal. Laboratory studies, including thyroid function tests, are within normal limits. In addition to a recommendation of psychotherapy, pharmacotherapy with buspirone is initiated. This medication is associated with which of the following properties?

- A. Antiseizure properties (3%)
- B. Efficacy in panic disorder (17%)
- C. Euphoric effects (5%)
- D. Muscle relaxant properties (12%)
- ✓ E. No risk of dependence (53%)
- F. Rapid onset of action (7%)

Omitted
Correct answer
E

53%
Answered correctly

01 sec
Time Spent

02/03/2020
Last Updated

Explanation

This patient's chronic anxiety about multiple issues and associated symptoms of muscle tension, impaired concentration, and fatigue are consistent with a diagnosis of **generalized anxiety disorder** (GAD). **Buspirone** is a **nonbenzodiazepine anxiolytic** used in the treatment of GAD that has **no risk of dependence** in contrast to the substantial risk associated with benzodiazepines.

Omitted
Correct answer
E

53%
Answered correctly

01 sec
Time Spent

02/03/2020
Last Updated

Explanation

This patient's chronic anxiety about multiple issues and associated symptoms of muscle tension, impaired concentration, and fatigue are consistent with a diagnosis of **generalized anxiety disorder** (GAD). **Buspirone** is a **nonbenzodiazepine anxiolytic** used in the treatment of GAD that has **no risk of dependence** in contrast to the substantial risk associated with benzodiazepines.

(Choices A, B, and D) Buspirone acts as a partial agonist of the $5HT_{1A}$ receptor. In contrast to benzodiazepines, which act at GABA-A receptors, buspirone primarily affects serotonin and has no muscle relaxant or anticonvulsant properties. Buspirone is also not effective in treating panic disorder.

(Choice C) Buspirone has fewer sedative and hypnotic effects compared to benzodiazepines and does not cause euphoria.

(Choice F) Buspirone is not useful in the acute setting because it requires up to 2 weeks for the anxiolytic effect to begin.

Educational objective:
Buspirone is a nonbenzodiazepine anxiolytic used to treat generalized anxiety disorder. It has a slow onset of action, lacks muscle relaxant or anticonvulsant properties, and carries no risk of dependence.

References

- Buspirone: what is it all about?
- Buspirone: back to the future.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Generalized anxiety disorder
Subject	System	Topic

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A 44-year-old man hospitalized for acute cholecystitis is being evaluated for anxiety and agitation. He underwent an open cholecystectomy without having any operative complications. Two days after admission, the patient experiences anxiety and tremulousness, and he becomes irritable, severely agitated, and verbally abusive to the nursing staff. He has no other medical problems. The patient does not use tobacco or illicit drugs but admits to drinking 6-8 beers daily for the last several years. He has no known drug allergies, and family history is insignificant. Blood pressure is 160/90 mm Hg and pulse is 110/min. Examination shows hand tremors bilaterally. Which of the following is the most appropriate pharmacotherapy for this patient?

- A. Baclofen
- B. Carbamazepine
- C. Chlorpromazine
- D. Haloperidol
- E. Chlordiazepoxide
- F. Phenobarbital
- G. Propranolol

Submit

A 44-year-old man hospitalized for acute cholecystitis is being evaluated for anxiety and agitation. He underwent an open cholecystectomy without having any operative complications. Two days after admission, the patient experiences anxiety and tremulousness, and he becomes irritable, severely agitated, and verbally abusive to the nursing staff. He has no other medical problems. The patient does not use tobacco or illicit drugs but admits to drinking 6-8 beers daily for the last several years. He has no known drug allergies, and family history is insignificant. Blood pressure is 160/90 mm Hg and pulse is 110/min. Examination shows hand tremors bilaterally. Which of the following is the most appropriate pharmacotherapy for this patient?

- A. Baclofen (3%)
- B. Carbamazepine (7%)
- C. Chlorpromazine (5%)
- D. Haloperidol (10%)
- ✓ E. Chlordiazepoxide (50%)
- F. Phenobarbital (12%)
- G. Propranolol (10%)

Omitted
Correct answer
E

50%
Answered correctly

01 sec
Time Spent

01/27/2020
Last Updated

Explanation

This patient's acute onset of tremulousness, agitation, and elevated pulse and blood pressure within 48 hours of admission is suggestive of

Explanation

This patient's acute onset of tremulousness, agitation, and elevated pulse and blood pressure within 48 hours of admission is suggestive of **alcohol withdrawal**. Alcohol is a CNS depressant that binds to the $GABA_A$ receptor complex, enhancing the inhibitory action of GABA (the major inhibitory neurotransmitter in the brain). Abrupt cessation of alcohol decreases inhibitory tone and results in CNS excitation. Alcohol withdrawal symptoms typically start within 8-12 hours after the last drink and include **insomnia, tremulousness, anxiety**, and **autonomic hyperactivity** (variable blood pressure, diaphoresis, and tachycardia). Alcohol withdrawal seizures can occur within 12-48 hours, and delirium tremens (disorientation, severe agitation, fever) typically begins within 48-96 hours.

Alcohol, barbiturates, and benzodiazepines have similar effects on GABA receptors and act by enhancing GABA inhibitory action. **Benzodiazepines** (eg, lorazepam, diazepam, chlordiazepoxide) are used as **first-line therapy** for psychomotor agitation associated with alcohol withdrawal and to prevent progression to seizures and delirium. Longer-acting benzodiazepines and those with active metabolites are preferred in the majority of patients due to self-tapering effects, resulting in a smoother course of withdrawal.

(Choice A) Baclofen is an agonist of GABA B receptors and is used to treat spastic conditions. It is less effective than benzodiazepines for treating alcohol withdrawal.

(Choice B) Carbamazepine may have a role in outpatient management of mild alcohol withdrawal, but there is insufficient evidence for its use in moderate to severe alcohol withdrawal.

(Choices C and D) Chlorpromazine and haloperidol are antipsychotic medications that lower the seizure threshold. They should not be used to treat alcohol withdrawal as these patients are already at significant risk for seizure.

(Choice F) Phenobarbital is a barbiturate anticonvulsant that enhances GABA activity. It is no longer used as first-line treatment for alcohol withdrawal because it has a worse safety profile than benzodiazepines.

(Choice G) The beta blocker propranolol can treat tremor, tachycardia, and hypertension, but it has not been shown to prevent development of seizures or delirium tremens. Treatment with benzodiazepines is the most crucial step in the management of alcohol withdrawal.

Educational objective:
Alcohol withdrawal should be considered in hospitalized patients who develop tremulousness, agitation, and elevated pulse and blood pressure within 48 hours following admission. Benzodiazepines act as a substitute for the effects of alcohol on GABA receptors, preventing alcohol

withdrawal and to prevent progression to seizures and delirium. Longer-acting benzodiazepines and those with active metabolites are preferred in the majority of patients due to self-tapering effects, resulting in a smoother course of withdrawal.

(Choice A) Baclofen is an agonist of GABA B receptors and is used to treat spastic conditions. It is less effective than benzodiazepines for treating alcohol withdrawal.

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(Choice G) The beta blocker propranolol can treat tremor, tachycardia, and hypertension, but it has not been shown to prevent development of seizures or delirium tremens. Treatment with benzodiazepines is the most crucial step in the management of alcohol withdrawal.

Educational objective:
Alcohol withdrawal should be considered in hospitalized patients who develop tremulousness, agitation, and elevated pulse and blood pressure within 48 hours following admission. Benzodiazepines act as a substitute for the effects of alcohol on GABA receptors, preventing alcohol withdrawal from occuring.

References

- Benzodiazepines for alcohol withdrawal.
- Alcohol withdrawal syndrome: benzodiazepines and beyond.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Alcohol withdrawal
Subject	System	Topic

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A 34-year-old woman with sleep problems comes to the office. Over the last year, she has had increasing difficulty falling asleep at night and is exhausted during the day. The patient does not use alcohol, tobacco, or illicit drugs. She has a family history of heart disease and depression. The patient has failed a number of nonpharmacological approaches, including cognitive-behavioral therapy for insomnia. She requests pharmacologic treatment and is prescribed a short course of zolpidem. Which of the following is the most likely mechanism of action of this medication?

A. Dopamine receptor antagonism
B. GABA receptor agonism
C. Histamine receptor antagonism
D. Melatonin receptor agonism
E. Orexin receptor antagonism
F. Serotonin receptor agonism

Submit

A 34-year-old woman with sleep problems comes to the office. Over the last year, she has had increasing difficulty falling asleep at night and is exhausted during the day. The patient does not use alcohol, tobacco, or illicit drugs. She has a family history of heart disease and depression. The patient has failed a number of nonpharmacological approaches, including cognitive-behavioral therapy for insomnia. She requests pharmacologic treatment and is prescribed a short course of zolpidem. Which of the following is the most likely mechanism of action of this medication?

- A. Dopamine receptor antagonism (1%)
- ✓ B. GABA receptor agonism (74%)
- C. Histamine receptor antagonism (1%)
- D. Melatonin receptor agonism (13%)
- E. Orexin receptor antagonism (6%)
- F. Serotonin receptor agonism (2%)

Omitted
Correct answer
B

74%
Answered correctly

01 sec
Time Spent

02/18/2020
Last Updated

Explanation

Zolpidem is a short-acting **nonbenzodiazepine** hypnotic agent. Other medications in this class include zaleplon and eszopiclone. Like benzodiazepines, these medications bind to the $GABA_A$ receptor at the benzodiazepine receptor site, where they act as **$GABA_A$ agonists**. However, they are chemically distinct from benzodiazepines, and their binding is more specific for certain receptor subtypes. As a result, nonbenzodiazepines are primarily **hypnotics** and do not produce the anxiolytic, muscle relaxant, or anticonvulsant effects associated with

Zolpidem is a short-acting **nonbenzodiazepine** hypnotic agent. Other medications in this class include zaleplon and eszopiclone. Like benzodiazepines, these medications bind to the $GABA_A$ receptor at the benzodiazepine receptor site, where they act as **$GABA_A$ agonists**. However, they are chemically distinct from benzodiazepines, and their binding is more specific for certain receptor subtypes. As a result, nonbenzodiazepines are primarily **hypnotics** and do not produce the anxiolytic, muscle relaxant, or anticonvulsant effects associated with benzodiazepines.

Nonbenzodiazepines cause similar side effects to benzodiazepines (eg, next-day somnolence, cognitive dysfunction, increased risk of falls in older adults). They should be used for the shortest time possible and at the lowest effective dose.

(Choice A) Dopamine receptor antagonism is the mechanism of action of antipsychotic medication (eg, haloperidol, risperidone).

(Choice C) Histamine receptor antagonism is the mechanism of action of antihistamines (eg, diphenhydramine). Although antihistamines are often used as over-the-counter sleep aids, there is little evidence for benefit in insomnia.

(Choice D) Melatonin receptor agonism is the mechanism of action of the insomnia medication ramelteon.

(Choice E) Orexin receptor antagonism is the mechanism of action of the insomnia medication suvorexant.

(Choice F) Serotonin receptor agonism is the mechanism of action of triptans used to treat migraine headaches and of psychedelics (eg, psilocybin, LSD).

Educational objective:
Nonbenzodiazepine medications (eg, zolpidem, zaleplon, eszopiclone) stimulate specific subtypes of $GABA_A$ receptors. As a result, nonbenzodiazepines are primarily hypnotics and do not produce the anxiolytic, muscle relaxant, or anticonvulsant effects associated with benzodiazepines.

References

- Randomised clinical trial of the effects of prolonged-release melatonin, temazepam and zolpidem on slow-wave activity during sleep in healthy people.
- Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline

A 46-year-old woman with confusion and fever is brought to the emergency department. She is disoriented, somnolent, and difficult to rouse. A friend who accompanies the patient says, "She sounded really anxious when I talked to her on the phone so I decided to check in on her. She was just lying on the couch and groaning when I got there. I hope she didn't overdose again—she's tried to before." On physical examination, the patient's skin is flushed, oral mucosa is dry, and pupils are dilated and poorly responsive to light. Which of the following drugs, if taken in overdose, would most likely cause this clinical presentation?

- A. Amitriptyline
- B. Diazepam
- C. Haloperidol
- D. Prazosin
- E. Propranolol
- F. Sertraline

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- ✓ A. Amitriptyline (69%)
- B. Diazepam (10%)
- C. Haloperidol (5%)
- D. Prazosin (4%)
- E. Propranolol (1%)
- F. Sertraline (8%)

Omitted
Correct answer
A

69%
Answered correctly

01 sec
Time Spent

01/15/2020
Last Updated

Explanation

Anticholinergic toxicity	
Symptom	Mechanism

Anticholinergic toxicity	
Symptom	**Mechanism**
"Hot as a hare" ↑ Body temperature	↓ Sweating leads to ↓ heat dissipation
"Dry as a bone" ↓ Secretions (eg, mucous membranes, sweat glands)	↓ Glandular secretion & smooth muscle contraction
"Red as a beet" Flushed skin	Superficial vasodilation from ↑ body heat
"Blind as a bat" Cycloplegia, mydriasis	Paralysis of ciliary muscle & iris sphincter
"Mad as a hatter" Altered mental status	Permeates blood-brain barrier & affects CNS pathways
"Full as a flask" Urinary retention Constipation	↓ Detrusor contraction & ↓ internal urethral sphincter relaxation ↓ Intestinal smooth muscle contraction
"Fast as a fiddle" Tachycardia	↓ Vagal tone at the sinoatrial node

This patient exhibits signs and symptoms of **anticholinergic toxicity**, which results from the inhibition of cholinergic neurotransmission at muscarinic receptors. Classic manifestations include **fever**, **delirium**, mucosal and axillary **dryness**, cutaneous **flushing**, nonreactive **mydriasis**, and **urinary retention**. Tachycardia and decreased bowel sounds are other common signs.

Anticholinergic toxicity is associated with numerous over-the-counter (eg, antihistamines, sleep aids, cold preparations) and prescription medications. **Tricyclic antidepressants** (TCAs) are commonly implicated, particularly ones with strong anticholinergic properties such as **amitriptyline**. When taken in excess, TCAs can also increase QRS duration, cause arrhythmias, and precipitate seizures.

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Anticholinergic toxicity is associated with numerous over-the-counter (eg, antihistamines, sleep aids, cold preparations) and prescription medications. **Tricyclic antidepressants** (TCAs) are commonly implicated, particularly ones with strong anticholinergic properties such as **amitriptyline**. When taken in excess, TCAs can also increase QRS duration, cause arrhythmias, and precipitate seizures.

(Choice B) Typical symptoms of benzodiazepine overdose include sedation, anterograde amnesia, and respiratory depression.

(Choice C) Haloperidol is a high-potency, first-generation antipsychotic (FGA) that primarily causes neurological side effects due to potent D2 antagonism; anticholinergic effects are more common with low-potency FGAs (eg, chlorpromazine).

(Choice D) Prazosin is an alpha-1 adrenergic blocker used to treat hypertension and urinary retention due to benign prostatic hyperplasia. Its major adverse effect is hypotension (especially postural hypotension).

(Choice E) Adverse effects associated with an overdose of a nonselective beta adrenergic blocker include bronchoconstriction, hypotension, and bradyarrhythmias.

(Choice F) An overdose of a selective serotonin reuptake inhibitor (eg, sertraline) may result in serotonin syndrome, which is characterized by agitated delirium, autonomic instability, seizures, myoclonus, hyperreflexia, and diaphoresis (not anhidrosis as in anticholinergic overdose).

Educational objective:
Anticholinergic toxicity is characterized by fever; confusion; cutaneous flushing; dry oral mucosa; and dilated, poorly reactive pupils. Tricyclic antidepressants, particularly amitriptyline, have strong anticholinergic effects.

References

- Central anticholinergic adverse effects and their measurement.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Anticholinergics
Subject	System	Topic

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A 24-year-old man is found unconscious in the basement of his house. His mother calls emergency responders and informs them that the patient has a history of substance abuse and was recently hospitalized for major depressive disorder. In the emergency department, the patient is found to be cyanotic and unresponsive to painful stimuli. Temperature is 36.7 C (98.1 F), blood pressure is 101/62 mm Hg, pulse is 61/min, and respirations are 4/min. His pupils are constricted and minimally responsive to light. Resuscitation efforts are initiated. The patient receives intravenous medication and regains consciousness 2 minutes later. The drug most likely used to treat this patient has the greatest affinity for which of the following receptors?

A. 5-HT
B. Delta
C. GABA A
D. GABA B
E. Kappa
F. Mu
G. NMDA

Submit

A 24-year-old man is found unconscious in the basement of his house. His mother calls emergency responders and informs them that the patient has a history of substance abuse and was recently hospitalized for major depressive disorder. In the emergency department, the patient is found to be cyanotic and unresponsive to painful stimuli. Temperature is 36.7 C (98.1 F), blood pressure is 101/62 mm Hg, pulse is 61/min, and respirations are 4/min. His pupils are constricted and minimally responsive to light. Resuscitation efforts are initiated. The patient receives intravenous medication and regains consciousness 2 minutes later. The drug most likely used to treat this patient has the greatest affinity for which of the following receptors?

- A. 5-HT (2%)
- B. Delta (0%)
- C. GABA A (4%)
- D. GABA B (0%)
- E. Kappa (1%)
- ✓ F. Mu (86%)
- G. NMDA (2%)

Omitted
Correct answer
F

86%
Answered correctly

01 sec
Time Spent

02/22/2020
Last Updated

Explanation

This patient's history of substance abuse, **miosis**, **profound sedation**, and **respiratory depression** with rapid reversal of signs/symptoms with

This patient's history of substance abuse, **miosis**, **profound sedation**, and **respiratory depression** with rapid reversal of signs/symptoms with antidotal therapy is consistent with an **opioid overdose**. Several opioid receptor subtypes, including mu, delta, and kappa, have been identified. Available opioid medications (eg, morphine, hydromorphone) produce therapeutic analgesic effects by binding to these receptors and modulating pain perception.

Naloxone is a pure **opioid receptor antagonist** devoid of any agonist properties. Although it antagonizes opioid effects at all receptor types, it has the **greatest affinity for mu receptors** (responsible for opioid-induced cardiorespiratory depression). Naloxone competes with opioid medications, displacing them from opioid receptors; it is therefore an ideal agent for **reversing opioid intoxication/overdose**. Reversal effects can occur within minutes, and the duration is dose dependent (usually 1-4 hours). Naloxone must be given parenterally because it is metabolically inactivated by the liver when administered orally.

(Choice A) Medications with an affinity for 5-HT (serotonin) receptors do not have a role in the treatment of opioid overdose. Cyproheptadine, a 5-HT1A and 5-HT2A antagonist, is an oral medication that can be used to treat serotonin syndrome. Ondansetron is a 5-HT3 antagonist that may be administered intravenously for nausea and vomiting.

(Choices B and E) Delta and kappa are also opioid receptors that modulate pain. Although naloxone does bind to these receptors, it binds to mu opioid receptors with greatest affinity.

(Choices C and D) GABA is the primary inhibitory neurotransmitter in the brain and is the target of many drugs. Benzodiazepines and barbiturates work by binding to specific sites on GABA A receptors to facilitate inhibitory effects of GABA. Flumazenil is a GABA A benzodiazepine receptor antagonist used to reverse benzodiazepine intoxication. Baclofen is an agonist at the GABA B receptor that acts as a skeletal muscle relaxant. This patient's miosis and profound respiratory depression are more indicative of opioid overdose than benzodiazepine or baclofen intoxication.

(Choice G) Glutamate is an excitatory neurotransmitter that binds to NMDA receptors. Ketamine, a general anesthetic, is an example of an NMDA receptor antagonist. Naloxone does not have effects on NMDA receptors.

Educational objective:
Naloxone is a pure opioid receptor antagonist used to treat opioid intoxication or overdose. Although it binds to mu, kappa, and delta opioid receptors, it has the greatest affinity for mu receptors (which mediate opioid-induced bradycardia and respiratory depression), making it an ideal agent for treating opioid intoxication.

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Naloxone is a pure opioid receptor antagonist used to treat opioid intoxication or overdose. Although it binds to mu, kappa, and delta opioid receptors, it has the greatest affinity for mu receptors (which mediate opioid-induced bradycardia and respiratory depression), making it an ideal agent for treating opioid intoxication.

References

- Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacological review.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Opioids
Subject	System	Topic

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A 31-year-old man is hospitalized after sustaining multiple injuries during a motor vehicle collision. The patient is not conscious initially, and no information is available regarding his medical history. Two days after initial hospitalization, he experiences palpitations and difficulty sleeping. Shortly thereafter, the patient suffers a generalized tonic-clonic seizure. When he recovers, he tells the physician that he usually takes medications for anxiety, bipolar disorder, and chronic low back pain. Temperature is 36.7 C (98.1 F), blood pressure is 129/82 mm Hg, pulse is 92/min, and respirations are 14/min. He appears anxious, tremulous, and diaphoretic. Withdrawal from which of the following medications is the most likely explanation for this patient's presentation?

A. Lamotrigine
B. Lithium
C. Lorazepam
D. Oxycodone
E. Quetiapine
F. Sertraline
G. Valproate

Submit

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- A. Lamotrigine (1%)
- B. Lithium (6%)
- ✓ C. Lorazepam (58%)
- D. Oxycodone (23%)
- E. Quetiapine (1%)
- F. Sertraline (2%)
- G. Valproate (5%)

Omitted
Correct answer
C

58%
Answered correctly

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Time Spent

02/01/2020
Last Updated

Explanation

This patient's presentation is consistent with **benzodiazepine withdrawal** (eg, lorazepam), which is most often characterized by **rebound**

This patient's presentation is consistent with **benzodiazepine withdrawal** (eg, lorazepam), which is most often characterized by **rebound anxiety, tremor, insomnia,** and **sympathetic hyperactivity** (eg, diaphoresis, palpitations). In severe cases, **psychotic symptoms** (eg, hallucinations, delusions), **seizures**, and even **death** may occur. Risk of withdrawal is greatest with short-acting agents (eg, alprazolam), prolonged use, and use of higher doses.

Benzodiazepines act on the $GABA_A$ receptor, enhancing the action of the natural ligand, GABA. The body adapts to chronic benzodiazepine exposure by downregulating the $GABA_A$ receptor, leading to tolerance, a phenomenon in which the same dose of a medication yields decreasing effects over time. This same adaptive downregulation process is responsible for the withdrawal syndrome when benzodiazepines are discontinued and the body is unable to balance opposing excitatory neurotransmitters. Benzodiazepine withdrawal is treated by starting a patient on a long-acting benzodiazepine (eg, diazepam) and planning for an extended, gradual taper.

(Choices A and G) The anticonvulsants lamotrigine and valproate are used in bipolar disorder for their mood-stabilizing properties. Withdrawal from these medications would not produce seizures in a patient without an underlying seizure disorder.

(Choices B and E) Withdrawal from lithium or quetiapine, when used to treat bipolar disorder, may be associated with a risk for manic relapse and nonspecific rebound psychiatric symptoms (eg, anxiety, restlessness). However, withdrawal from these medications would not explain this patient's symptoms or seizure.

(Choice D) Opioid (eg, oxycodone) withdrawal is characterized by nausea, vomiting, diarrhea, lacrimation, dilated pupils, and piloerection.

(Choice F) Selective serotonin reuptake inhibitor (eg, sertraline) withdrawal presents with rebound anxiety/dysphoria, dizziness, headache, and nausea.

Educational objective:
Benzodiazepine withdrawal is characterized by anxiety, tremor, insomnia, and sympathetic hyperactivity (eg, diaphoresis, palpitations). Severe benzodiazepine withdrawal may also be accompanied by psychosis, seizures, or death.

References

- Benzodiazepine harm: how can it be reduced?
- Sedative-hypnotic drug withdrawal syndrome: recognition and treatment.

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A 42-year-old woman with a history of schizophrenia is brought to the clinic by her parents after attempting to drink rubbing alcohol in response to voices telling her to kill herself. The patient believes that a television newscaster is sending her secret messages and that the devil injects her with poison at night while she is sleeping. She first developed symptoms at age 23 and has had 7 previous psychiatric hospitalizations and 2 suicide attempts. Trials of haloperidol, risperidone, and olanzapine have yielded minimal improvement. Her medical conditions include hypertension and mild obesity. Physical examination is normal. Medication therapy with clozapine is initiated. Which of the following should be regularly monitored in this patient?

- A. Absolute neutrophil count
- B. Clozapine blood level
- C. Creatinine level
- D. ECG
- E. Liver function
- F. Platelet count
- G. Prolactin level
- H. Thyroid function

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- ✓ A. Absolute neutrophil count (83%)
- B. Clozapine blood level (1%)
- C. Creatinine level (1%)
- D. ECG (2%)
- E. Liver function (4%)
- F. Platelet count (4%)
- G. Prolactin level (1%)
- H. Thyroid function (1%)

Omitted
Correct answer
A

83%
Answered correctly

01 sec
Time Spent

01/13/2020
Last Updated

Explanation

Clozapine treatment guidelines	
Indications	• Treatment-resistant schizophrenia • Schizophrenia associated with suicidality
Adverse effects	• Agranulocytosis • Seizures • Myocarditis • Metabolic syndrome

The second-generation antipsychotic **clozapine** is the only antipsychotic that has consistently shown superior efficacy in **treatment-resistant schizophrenia** and schizophrenia associated with persistent suicidality. Clozapine has affinity for multiple dopamine and serotonin receptors, but the precise pharmacological mechanism responsible for its superior efficacy is unknown. Clozapine binds loosely and transiently to dopamine D2 receptors, causing significantly fewer extrapyramidal symptoms compared to first-generation antipsychotics.

Neutropenia (<1000 cells/mm^3) and the potential for life-threatening **agranulocytosis** are the major adverse effects of clozapine. The risk of agranulocytosis is approximately 1%; therefore, treatment requires **regular monitoring** of the patient's **absolute neutrophil count**. Treatment should be stopped if neutropenia occurs. Seizures and myocarditis are other important adverse effects that require provider vigilance.

(Choice B) Clozapine plasma levels can be checked after an initial target dose is reached, but further dosage adjustments are usually based on clinical response. Clozapine levels are not regularly monitored.

(Choices C and H) Creatinine levels and thyroid function tests should be monitored in patients taking lithium due to this drug's potential to adversely affect thyroid and renal function.

(Choice D) Although a baseline ECG is required and physicians should be alert to the development of cardiovascular symptoms suggestive of myocarditis, routine ECGs are not required. Among the second-generation antipsychotics, ziprasidone is most often noted for causing a prolonged QT interval.

(Choices E and F) Liver function tests may be mildly elevated with the use of many psychotropic medications, including antipsychotics and anticonvulsants; thrombocytopenia can be caused by some anticonvulsants. However, routine monitoring of liver function tests and platelets is not

agranulocytosis is approximately 1%; therefore, treatment requires **regular monitoring** of the patient's **absolute neutrophil count**. Treatment should be stopped if neutropenia occurs. Seizures and myocarditis are other important adverse effects that require provider vigilance.

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(Choices E and F) Liver function tests may be mildly elevated with the use of many psychotropic medications, including antipsychotics and anticonvulsants; thrombocytopenia can be caused by some anticonvulsants. However, routine monitoring of liver function tests and platelets is not required with clozapine.

(Choice G) Prolactin levels are not routinely monitored. Among the second-generation antipsychotics, risperidone has been associated with a greater risk of prolactin elevation.

Educational objective:
Patients treated with clozapine are required to have regular monitoring of the absolute neutrophil count due to the risk of life-threatening agranulocytosis.

References

- Medical management of patients on clozapine: a guide for internists.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Antipsychotics
Subject	System	Topic

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A 35-year-old man was hospitalized for a psychotic episode in which he heard voices of God and the devil and believed that his family was plotting to kill him. He improved rapidly with medication therapy and was discharged. Three weeks later, the patient comes to the emergency department due to generalized muscle stiffness and shaking of his right hand. He has no other medical history and takes no other medications. Temperature is 36.7 C (98 F), blood pressure is 110/80 mm Hg, pulse is 68/min, and respirations are 14/min. On mental status examination, he is alert and oriented with mild paranoia but no auditory hallucinations. Which of the following is the best treatment for this patient's current symptoms?

A. Benztropine
B. Dantrolene
C. Diazepam
D. Haloperidol
E. Levodopa
F. Propranolol

Submit

A 35-year-old man was hospitalized for a psychotic episode in which he heard voices of God and the devil and believed that his family was plotting to kill him. He improved rapidly with medication therapy and was discharged. Three weeks later, the patient comes to the emergency department due to generalized muscle stiffness and shaking of his right hand. He has no other medical history and takes no other medications. Temperature is 36.7 C (98 F), blood pressure is 110/80 mm Hg, pulse is 68/min, and respirations are 14/min. On mental status examination, he is alert and oriented with mild paranoia but no auditory hallucinations. Which of the following is the best treatment for this patient's current symptoms?

- ✓ A. Benztropine (52%)
- B. Dantrolene (19%)
- C. Diazepam (8%)
- D. Haloperidol (8%)
- E. Levodopa (6%)
- F. Propranolol (4%)

Omitted
Correct answer
A

52%
Answered correctly

01 sec
Time Spent

01/24/2020
Last Updated

Explanation

Drug-induced parkinsonism	
Etiology	• D2 receptor blockers ∘ Antipsychotics (First-generation > second-generation)

Drug-induced parkinsonism	

Etiology	• D2 receptor blockers
	  ◦ Antipsychotics (First-generation > second-generation)
	  ◦ Antiemetics/gastric motility agents (prochlorperazine, metoclopramide)

Symptoms	• Prominent rigidity & bradykinesia (slowed movement, decreased arm swing) • Tremor (rest & postural) • Masked facies
Management	• Decrease or discontinue offending medication • Anticholinergics (trihexyphenidyl, benztropine)

This patient's psychotic episode was most likely treated with an antipsychotic, and his current symptoms are consistent with **drug-induced parkinsonism**, an extrapyramidal side effect of antipsychotics. Symptoms include **rigidity** (may be experienced as subjective stiffness), **resting/postural tremor**, **masked facies**, and **bradykinesia** and typically occur within the first 3 months of drug initiation. Other extrapyramidal side effects of antipsychotic medications include acute dystonia (sudden, sustained contraction of muscle groups) and akathisia (subjective restlessness and inability to sit still).

Drug-induced parkinsonism is caused by **dopamine (D2) receptor blockade** in the **nigrostriatal pathway**. If the antipsychotic cannot be reduced or discontinued, drug-induced parkinsonism is best treated with a centrally acting **anticholinergic agent** (eg, benztropine). Levodopa should not be used to treat antipsychotic-induced parkinsonism as it can exacerbate or even precipitate psychosis **(Choice E)**.

(Choice B) Dantrolene is a direct-acting skeletal muscle relaxant used in the treatment of neuroleptic malignant syndrome (NMS). NMS presents with diffuse muscle rigidity, high fever, sympathetic hyperactivity (eg, hypertension, tachycardia), and altered mental status and is unlikely in this oriented, afebrile patient with normal vital signs.

(Choices C and F) The benzodiazepine diazepam and the beta blocker propranolol may both be used in the treatment of akathisia. Akathisia is characterized by subjective restless and an inability to sit still rather than rigidity and tremor, as seen in this patient.

(Choice D) Haloperidol is a first-generation antipsychotic and potent D2 blocker that frequently causes extrapyramidal symptoms, including drug-induced parkinsonism. Its use would only exacerbate the patient's parkinsonian symptoms. Use of a second-generation antipsychotic with

side effects of antipsychotic medications include acute dystonia (sudden, sustained contraction of muscle groups) and akathisia (subjective restlessness and inability to sit still).

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(Choice D) Haloperidol is a first-generation antipsychotic and potent D2 blocker that frequently causes extrapyramidal symptoms, including drug-induced parkinsonism. Its use would only exacerbate the patient's parkinsonian symptoms. Use of a second-generation antipsychotic with minimal D2 blockade would be a reasonable long-term alternative if the patient were taking a first-generation antipsychotic.

Educational objective:
Drug-induced parkinsonism is an extrapyramidal side effect caused by medications that block D2 receptors (eg, antipsychotics). Management strategies include decreasing or discontinuing the offending medication and treatment with an anticholinergic medication.

References

- Drug-induced parkinsonism.
- Drug-induced extrapyramidal syndromes: implications for contemporary practice.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Antipsychotics
Subject	System	Topic

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A 23-year-old woman comes to the emergency department due to chest pain, dyspnea, palpitations, perioral numbness, and sweating. She is extremely anxious and explains that her symptoms came on suddenly for no apparent reason. The patient has had similar episodes 2 or 3 times a week for the past several months. Her blood pressure is 150/90 mm Hg, pulse is 100/min, and respirations are 28/min. Cardiac enzymes are normal, and an ECG shows normal sinus rhythm with no ST-segment or T-wave abnormalities. The patient is diagnosed with panic disorder. She receives medication and feels better within an hour. Which of the following best describes the mechanism of action of the medication she received?

A. Affects G protein signal transduction
B. Alters GABA metabolism
C. Binds allosterically to the GABA receptor
D. Competes with GABA at its binding site
E. Physically blocks the ion channel lumen
F. Upregulates GABA receptor density

Submit

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- A. Affects G protein signal transduction (3%)
- B. Alters GABA metabolism (3%)
- ✓ C. Binds allosterically to the GABA receptor (76%)
- D. Competes with GABA at its binding site (7%)
- E. Physically blocks the ion channel lumen (3%)
- F. Upregulates GABA receptor density (6%)

Omitted
Correct answer
C

76%
Answered correctly

01 sec
Time Spent

06/20/2020
Last Updated

Explanation

GABA A receptor

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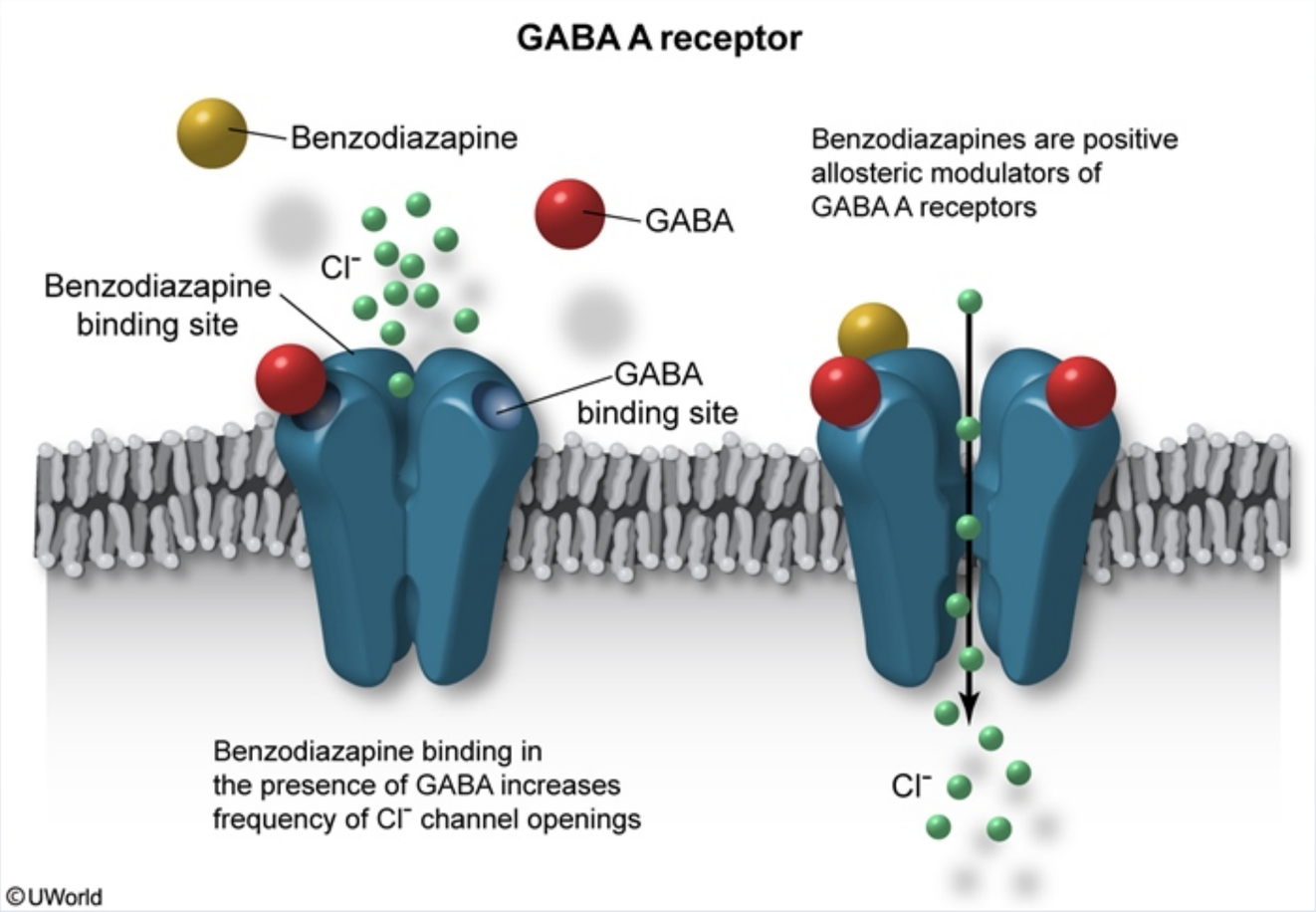

This patient exhibits classic symptoms of a panic attack (abrupt and unexpected onset of characteristic physical symptoms and negative medical workup). She most likely received a benzodiazepine, a medication commonly used in emergency settings because it provides rapid relief of acute anxiety.

Benzodiazepines work at the $GABA_A$ (γ-aminobutyric acid) receptor complex. **GABA** is the **main inhibitory neurotransmitter** in the central nervous system and is synthesized from glutamate using glutamate decarboxylase. The $GABA_A$ receptor complex consists of 5 subunits and a

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Benzodiazepines work at the $GABA_A$ (γ-aminobutyric acid) receptor complex. **GABA** is the **main inhibitory neurotransmitter** in the central nervous system and is synthesized from glutamate using glutamate decarboxylase. The $GABA_A$ receptor complex consists of 5 subunits and a central chloride ion channel, with different binding sites for GABA and various drugs (eg, benzodiazepines, barbiturates). **Benzodiazepines** act by binding to the benzodiazepine binding site, which **allosterically modulates** the **binding of GABA**, resulting in an **increased** frequency of **chloride ion channel opening**. The influx of chloride ions into the neurons causes neuronal hyperpolarization and inhibition of the action potential. Barbiturates act at a separate allosteric site and work by prolonging the duration of channel openings in response to GABA and, at higher doses, as $GABA_A$ receptor agonists.

(Choice A) $GABA_B$ receptors mediate their actions using G proteins. The skeletal muscle relaxant baclofen is an example of a drug that works as a $GABA_B$ receptor agonist. Benzodiazepines work at the $GABA_A$ receptor.

(Choice B) Benzodiazepines do not alter GABA metabolism. Certain anti-epileptic medications, including valproic acid and vigabatrin, function to reduce GABA catabolism.

(Choice D) Benzodiazepines do not function through direct activation of the $GABA_A$ receptor. Instead, they work as positive allosteric modulators that promote an increased frequency of channel openings in response to GABA stimulation.

(Choice E) Benzodiazepines do not function through blockage of the $GABA_A$ receptor lumen. Examples of drugs that directly block the lumen of ion channels include amiloride (which affects epithelial sodium channels in the distal portions of the nephron) and verapamil (a calcium channel blocker).

(Choice F) Prolonged benzodiazepine use has been shown to cause downregulation of $GABA_A$ receptors and may be one of the mechanisms by which benzodiazepine tolerance develops.

Educational objective:
Benzodiazepines act by binding to the benzodiazepine binding site, which allosterically modulates the binding of GABA, resulting in an increased

potential. Barbiturates act at a separate allosteric site and work by prolonging the duration of channel openings in response to GABA and, at higher doses, as $GABA_A$ receptor agonists.

(Choice A) $GABA_B$ receptors mediate their actions using G proteins. The skeletal muscle relaxant baclofen is an example of a drug that works as a $GABA_B$ receptor agonist. Benzodiazepines work at the $GABA_A$ receptor.

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Educational objective:
Benzodiazepines act by binding to the benzodiazepine binding site, which allosterically modulates the binding of GABA, resulting in an increased frequency of chloride ion channel opening. The *influx of chloride ions* into the neurons causes neuronal hyperpolarization and inhibition of the action potential.

References

- Benzodiazepine pharmacology and central nervous system-mediated effects.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Benzodiazepines
Subject	System	Topic

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A 23-year-old woman comes to the office describing restlessness in her legs and inability to lie or sit still. The patient was diagnosed with schizophrenia a month ago and medication therapy was initiated. Her dose was increased after 2 weeks. She says, "I haven't heard any voices since a few days after the medication was increased." Blood pressure is 140/90 mm Hg and pulse is 90/min. The patient is alert, oriented, fidgety, and anxious. Which of the following is the most likely diagnosis in this patient?

A. Acute dystonia
B. Akathisia
C. Drug-induced parkinsonism
D. Neuroleptic malignant syndrome
E. Psychotic agitation
F. Tardive dyskinesia

Submit

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- A. Acute dystonia (6%)
- ✓ B. Akathisia (71%)
- C. Drug-induced parkinsonism (7%)
- D. Neuroleptic malignant syndrome (2%)
- E. Psychotic agitation (3%)
- F. Tardive dyskinesia (8%)

Omitted
Correct answer
B

71%
Answered correctly

01 sec
Time Spent

02/17/2020
Last Updated

Explanation

Important antipsychotic side effects	
Extrapyramidal side effects	• Acute dystonic reaction: Sudden-onset, sustained muscle contractions • Akathisia: Subjective restlessness with inability to sit still • Drug-induced parkinsonism: Tremor, rigidity, bradykinesia, masked facies

Important antipsychotic side effects	
Extrapyramidal side effects	• Acute dystonic reaction: Sudden-onset, sustained muscle contractions • Akathisia: Subjective restlessness with inability to sit still • Drug-induced parkinsonism: Tremor, rigidity, bradykinesia, masked facies
Tardive dyskinesia	• Involuntary movements after chronic use (eg, lip smacking, choreoathetoid movements)
Neuroleptic malignant syndrome	• Fever, rigidity, mental status changes, autonomic instability

This patient is experiencing **akathisia**, a type of extrapyramidal side effect associated with antipsychotic treatment. Akathisia ranges from mild subjective feelings of tension to marked physical restlessness (which can be extremely distressing for patients). It typically presents days to weeks after initiating antipsychotic treatment or increasing the dose. Patients describe an inability to sit or stand in one position and may pace frequently or demonstrate other restless behaviors. Treatment options include decreasing the antipsychotic dose (if feasible) or treating with a beta blocker or benzodiazepines.

(Choice A) Acute dystonia is an extrapyramidal side effect characterized by acute onset of involuntary muscle contraction of the neck, mouth, tongue, or eye muscles. It occurs within hours to days of antipsychotic use, especially with rapid dose escalation of high-potency, first-generation antipsychotics (eg, haloperidol), and is treated with anticholinergic medication (eg, diphenhydramine, benztropine).

(Choice C) Drug-induced parkinsonism is an extrapyramidal side effect that presents with cogwheel rigidity, masked facies, bradykinesia, tremor, and decreased arm swing. Treatment is usually with anticholinergics (eg, benztropine).

(Choice D) Neuroleptic malignant syndrome is an acute, potentially fatal reaction to antipsychotic medications. Patients have hyperthermia, sympathetic hyperactivity (eg, tachycardia, diaphoresis), severe "lead pipe" rigidity, and altered mental status.

(Choice E) This patient reports that her auditory hallucinations have resolved and shows no other signs of psychosis. The physical restlessness of akathisia may be mistaken for psychotic agitation. It is important to differentiate the two etiologies as increasing the antipsychotic dose will further exacerbate akathisia.

(Choice F) Tardive dyskinesia is an involuntary and potentially irreversible movement disorder due to prolonged antipsychotic exposure (typically years). Characteristic movements include lip smacking, biting, grimacing, tongue protrusions, and choreoathetoid movements of the head, limbs

This patient is experiencing **akathisia**, a type of extrapyramidal side effect associated with antipsychotic treatment. Akathisia ranges from mild subjective feelings of tension to marked physical restlessness (which can be extremely distressing for patients). It typically presents days to weeks after initiating antipsychotic treatment or increasing the dose. Patients describe an inability to sit or stand in one position and may pace frequently or demonstrate other restless behaviors. Treatment options include decreasing the antipsychotic dose (if feasible) or treating with a beta blocker or benzodiazepines.

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(Choice D) Neuroleptic malignant syndrome is an acute, potentially fatal reaction to antipsychotic medications. Patients have hyperthermia, sympathetic hyperactivity (eg, tachycardia, diaphoresis), severe "lead pipe" rigidity, and altered mental status.

(Choice E) This patient reports that her auditory hallucinations have resolved and shows no other signs of psychosis. The physical restlessness of akathisia may be mistaken for psychotic agitation. It is important to differentiate the two etiologies as increasing the antipsychotic dose will further exacerbate akathisia.

(Choice F) Tardive dyskinesia is an involuntary and potentially irreversible movement disorder due to prolonged antipsychotic exposure (typically years). Characteristic movements include lip smacking, biting, grimacing, tongue protrusions, and choreoathetoid movements of the head, limbs, and trunk.

Educational objective:
Akathisia is an extrapyramidal side effect of antipsychotic medication characterized by inner restlessness and an inability to sit or stand in one position. Treatment involves a reduction in the antipsychotic dose, if possible, or the addition of a beta blocker or benzodiazepine.

References

- Drug-induced akathisia.
- Revisiting antipsychotic-induced akathisia: current issues and prospective challenges.

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A 36-year-old woman comes to the office for follow-up of a mood disorder. The patient has a history of several depressive episodes that started in her twenties. Two years ago, she was hospitalized after staying up for several nights without sleeping and claiming that she had special powers to "end global poverty and climate change." Her symptoms responded well to treatment and she has remained on the same drug regimen since then. However, the patient now has new-onset constipation, dry skin, and hair loss. She is also concerned about a weight gain of 2.27 kg (5 lb) over the last 3-4 months despite eating healthy, low-calorie foods. Blood pressure is 110/70 mm Hg and pulse is 55/min. The patient appears tired, but physical examination is otherwise normal. The diagnosis is established and her current condition is attributed to adverse effects from one of her medications. Which of the following is the most likely culprit drug?

A. Carbamazepine
B. Citalopram
C. Clozapine
D. Lamotrigine
E. Lithium
F. Risperidone
G. Trazodone

Submit

A 36-year-old woman comes to the office for follow-up of a mood disorder. The patient has a history of several depressive episodes that started in her twenties. Two years ago, she was hospitalized after staying up for several nights without sleeping and claiming that she had special powers to "end global poverty and climate change." Her symptoms responded well to treatment and she has remained on the same drug regimen since then. However, the patient now has new-onset constipation, dry skin, and hair loss. She is also concerned about a weight gain of 2.27 kg (5 lb) over the last 3-4 months despite eating healthy, low-calorie foods. Blood pressure is 110/70 mm Hg and pulse is 55/min. The patient appears tired, but physical examination is otherwise normal. The diagnosis is established and her current condition is attributed to adverse effects from one of her medications. Which of the following is the most likely culprit drug?

- A. Carbamazepine (3%)
- B. Citalopram (3%)
- C. Clozapine (15%)
- D. Lamotrigine (3%)
- ✓ E. Lithium (64%)
- F. Risperidone (9%)
- G. Trazodone (1%)

Omitted
Correct answer
E

64%
Answered correctly

02 secs
Time Spent

03/20/2020
Last Updated

Explanation

Explanation

Mood stabilizers in bipolar disorder		
	Indications	**Adverse effects**
Lithium	• Manic & depressive features	• Diabetes insipidus • Hypothyroidism • Tremor • Ebstein anomaly (teratogenic)
Valproate	• Manic features	• Hepatotoxicity • Neural tube defects (teratogenic)
Carbamazepine	• Manic features	• Aplastic anemia • SIADH • Neural tube defects (teratogenic)
Lamotrigine	• Depressive features	• Benign rash • Stevens-Johnson syndrome

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

This patient's weight gain, hair loss, and mild bradycardia are most likely due to lithium-induced hypothyroidism. **Lithium** is a mood stabilizer primarily used in the treatment of bipolar disorder. It can cause **hypothyroidism** by interfering with normal synthesis and release of thyroid hormone. The compensatory increase in TSH release by the pituitary can lead to goiter in some patients. Lithium-induced hypothyroidism is treated with standard levothyroxine (T4) replacement and does not require discontinuation of lithium therapy.

Long-term lithium therapy is also associated with adverse effects on renal function (eg, **nephrogenic diabetes insipidus**, chronic tubulointerstitial nephropathy), requiring regular monitoring of blood lithium levels and renal function (blood urea nitrogen and creatinine). Lithium use during

pregnancy has been associated with **Ebstein anomaly** of the tricuspid valve, but the absolute risk is small.

(Choices A and D) Carbamazepine and lamotrigine are anticonvulsants that are also used as mood stabilizers in bipolar disorder. Carbamazepine can cause aplastic anemia. Lamotrigine is associated with a risk of rash, including potentially life-threatening Stevens-Johnson syndrome.

(Choice B) Citalopram is a selective serotonin reuptake inhibitor (SSRI) antidepressant. Sexual dysfunction is the most common long-term side effect. SSRIs are not used as monotherapy in bipolar disorder and are not associated with hypothyroidism.

(Choice C) Clozapine, a second-generation antipsychotic indicated for treatment-refractory schizophrenia, is associated with agranulocytosis and requires regular monitoring of the absolute neutrophil count. Although clozapine can cause weight gain and constipation, it is not a first-line treatment for mood disorders and would not explain this patient's other hypothyroid features (eg, dry skin, hair loss, bradycardia).

(Choice F) Risperidone is a second-generation antipsychotic that can cause weight gain and hyperprolactinemia (eg, galactorrhea, amenorrhea). It is not associated with hypothyroidism.

(Choice G) Trazodone is an antidepressant that has significant sedating effects and is most commonly used to treat depression-related insomnia. Other adverse effects include priapism (prolonged painful erection) and anticholinergic effects (eg, dry mouth, constipation).

Educational objective:
Hypothyroidism and nephrogenic diabetes insipidus are the most common adverse effects of long-term lithium therapy. Serum TSH and renal function (blood urea nitrogen and creatinine) should be monitored routinely.

References

- Spectrum of lithium induced thyroid abnormalities: a current perspective.
- Lithium side effects and toxicity: prevalence and management strategies.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Hypothyroidism
Subject	System	Topic

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A 24-year-old man is hospitalized after a violent episode in which he destroyed his television with a baseball bat. Over the past year, the patient was convinced that people on television were monitoring his thoughts and movements and that certain newscasters were laughing at him. At night, he was unable to sleep and reported hearing the voices of demons threatening to kill him. The patient was diagnosed with schizophrenia and initially treated with chlorpromazine. He now is reluctant to take the medication, saying, "I don't like how it makes me feel." His medication is subsequently changed to fluphenazine. Compared to the patient's initial treatment, fluphenazine is more likely to cause which of the following?

A. Constipation
B. Dizziness
C. Dry mouth
D. Hyperglycemia
E. Muscular rigidity
F. Sedation
G. Urinary retention

Submit

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A. Constipation (2%)
B. Dizziness (3%)
C. Dry mouth (7%)
D. Hyperglycemia (10%)
✓ E. Muscular rigidity (60%)
F. Sedation (11%)
G. Urinary retention (3%)

Omitted
Correct answer
E

60%
Answered correctly

02 secs
Time Spent

01/28/2020
Last Updated

Explanation

First-generation antipsychotics side effects		

First-generation antipsychotics side effects		
Type	**Side Effects**	**Examples**
Low-potency (non-neurological)	• Sedation (histaminergic blockade) • Anticholinergic side effects (cholinergic blockade) • Orthostatic hypotension (alpha-1 adrenergic blockade)	• Chlorpromazine • Thioridazine
High-potency (neurological)	Extrapyramidal symptoms: • Acute dystonia • Akathisia • Parkinsonism	• Haloperidol • Fluphenazine

First-generation antipsychotics (FGAs), also known as typical or conventional antipsychotics, are effective in treating schizophrenia and psychosis due to other causes. FGAs are classified according to potency, which refers to the dose required to produce an effect. **Low-potency FGAs** primarily cause **histaminergic**, **cholinergic**, and **noradrenergic blockade** side effects. These drugs are highly sedating and often cause anticholinergic side effects and orthostatic hypotension. **High-potency FGAs** are associated primarily with **extrapyramidal symptoms** (eg, dystonia, akathisia, parkinsonism) due to potent D2 dopamine receptor antagonism in the nigrostriatal pathway.

This patient's medication was changed from a low-potency FGA (chlorpromazine) to a high-potency FGA (fluphenazine). Muscular rigidity, an extrapyramidal side effect, is seen in drug-induced parkinsonism; it is more likely to occur with a high-potency agent.

(Choices A, C, and G) Constipation, dry mouth, and urinary retention are anticholinergic side effects due to cholinergic receptor blockade. They are more common with low-potency antipsychotics. Other anticholinergic side effects include blurred vision and impaired cognitive function.

(Choice B) Dizziness and orthostatic hypotension are due to alpha-1 adrenergic blockade and are more common with low-potency FGAs. Orthostatic hypotension is particularly problematic in the elderly due to the risk of falls.

(Choice D) Hyperglycemia is a metabolic side effect seen more commonly with second-generation antipsychotics.

(Choice F) Sedation is due to histamine receptor blockade that is more common with low-potency antipsychotics.

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(Choice D) Hyperglycemia is a metabolic side effect seen more commonly with second-generation antipsychotics.

(Choice F) Sedation is due to histamine receptor blockade that is more common with low-potency antipsychotics.

Educational objective:
First-generation antipsychotics can be classified according to high or low potency and have characteristic side effect profiles. Low-potency antipsychotics are more likely to cause sedation, anticholinergic side effects, and orthostatic hypotension. High-potency antipsychotics are more likely to cause extrapyramidal symptoms (eg, dystonia, akathisia, parkinsonism).

References

- Fluphenazine versus low-potency first-generation antipsychotic drugs for schizophrenia.
- Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Antipsychotics
Subject	System	Topic

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A 46-year-old woman comes to the office for follow-up after an episode of alcoholic pancreatitis. She was hospitalized 4 weeks ago for abdominal pain and concurrently underwent treatment with benzodiazepines for alcohol withdrawal. Prior to hospitalization, the patient was drinking 3 L of boxed wine daily; however, she has remained abstinent since discharge. She is interested in medication for her alcohol use disorder, but lives alone and is worried that her cravings will overwhelm her self control. A medication with which of the following mechanisms of action would be most effective in this patient?

A. Aldehyde dehydrogenase inhibition

B. Antagonism at postsynaptic dopamine receptors

C. Mu-opioid receptor blockade

D. Partial agonism at nicotinic acetylcholine receptors

E. Serotonin reuptake inhibition

Submit

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A. Aldehyde dehydrogenase inhibition (59%)

B. Antagonism at postsynaptic dopamine receptors (3%)

✓ C. Mu-opioid receptor blockade (28%)

D. Partial agonism at nicotinic acetylcholine receptors (5%)

E. Serotonin reuptake inhibition (2%)

Omitted
Correct answer
C

28%
Answered correctly

01 sec
Time Spent

01/27/2020
Last Updated

Explanation

In addition to psychosocial interventions (eg, motivational interviewing, Alcoholics Anonymous), several medications are available to treat **alcohol use disorder**, including naltrexone and acamprosate. **Naltrexone blocks the mu-opioid receptor** and inhibits the rewarding and reinforcing effects of alcohol, helping to reduce cravings and improving motivation to quit. The long-acting **depot form** (given as monthly injections) is useful for patients at risk for nonadherence with daily administration. Acamprosate, another abstinence-promoting drug, works by modulating glutamate neurotransmission at the N-methyl-D-aspartate receptor.

In addition to psychosocial interventions (eg, motivational interviewing, Alcoholics Anonymous), several medications are available to treat **alcohol use disorder**, including naltrexone and acamprosate. **Naltrexone blocks the mu-opioid receptor** and inhibits the rewarding and reinforcing effects of alcohol, helping to reduce cravings and improving motivation to quit. The long-acting **depot form** (given as monthly injections) is useful for patients at risk for nonadherence with daily administration. Acamprosate, another abstinence-promoting drug, works by modulating glutamate neurotransmission at the N-methyl-D-aspartate receptor.

(Choice A) The aldehyde dehydrogenase inhibitor disulfiram is considered a second-line treatment for alcohol use disorder because of poorer efficacy (effectiveness depends on supervised administration). When alcohol is ingested by a patient taking disulfiram, acetaldehyde accumulates and causes unpleasant adverse effects (eg, nausea, vomiting, flushing, sweating, headache).

(Choice B) Antagonism at postsynaptic dopamine receptors is the mechanism of action of antipsychotic medications. Antipsychotics are not effective in treating alcohol use disorder.

(Choice D) Varenicline acts as a partial neuronal nicotinic receptor agonist and prevents the nicotine stimulation of the mesolimbic dopamine system associated with nicotine addiction.

(Choice E) Serotonin reuptake inhibition is the mechanism of action of selective serotonin reuptake inhibitor antidepressants. Although they have shown some efficacy in reducing alcohol use in depressed patients with alcoholism, they are not useful for alcohol cessation in patients without comorbid depression.

Educational objective:
The opioid antagonist naltrexone is a first-line pharmacotherapy for moderate-to-severe alcohol use disorder, and works by preventing the reinforcing effects of alcohol use.

References

- Alcohol use disorders.
- Pharmacotherapy for alcohol dependence: status of current treatments.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Alcohol use disorder
Subject	System	Topic

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A 34-year-old man is brought to the emergency department due to a severe headache and blurry vision. His symptoms began suddenly after having lunch at a new Italian deli in his neighborhood. The patient says he "ate a sandwich with lots of fancy meats and cheeses" and drank an iced tea. His medical history is significant for treatment-resistant major depressive disorder. He has no known medication or food allergies. Blood pressure is 210/130 mm Hg and heart rate is 110/min. On physical examination, he appears tremulous and diaphoretic. The medication used to treat this patient's depression most likely affects which of the following steps of monoamine neurotransmission?

- A. Binding to postsynaptic monoamine receptors
- B. Monoamine breakdown
- C. Presynaptic nonselective monoamine uptake
- D. Presynaptic selective dopamine uptake
- E. Presynaptic selective norepinephrine uptake
- F. Presynaptic selective serotonin uptake

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- A. Binding to postsynaptic monoamine receptors (4%)
- ✓ B. Monoamine breakdown (73%)
- C. Presynaptic nonselective monoamine uptake (10%)
- D. Presynaptic selective dopamine uptake (1%)
- E. Presynaptic selective norepinephrine uptake (3%)
- F. Presynaptic selective serotonin uptake (6%)

Omitted
Correct answer
B

73%
Answered correctly

01 sec
Time Spent

02/17/2020
Last Updated

Explanation

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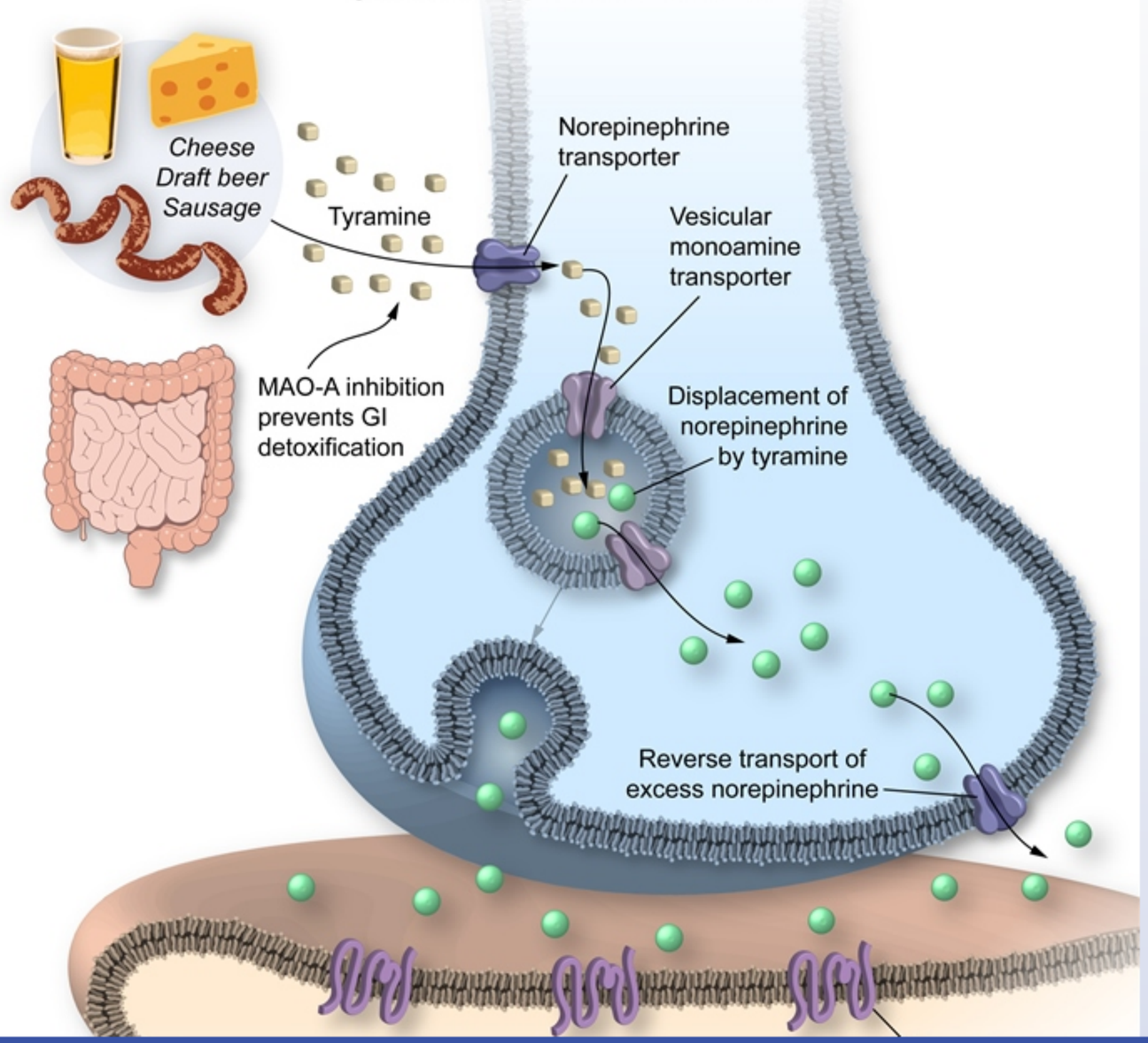
Tyramine hypertensive crisis



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↑ Sympathetic activity & hypertension

This patient is experiencing a **hypertensive emergency** (eg, severe hypertension, headache, blurry vision) and has signs of excessive sympathetic activity (eg, tachycardia, diaphoresis, tremors), most likely due to a food-drug interaction between **tyramine-containing foods** (eg, aged cheeses, cured meats, draft beer) and a **monoamine oxidase (MAO) inhibitor**.

MAO inhibitors increase the availability of all 3 major monoamines (eg, dopamine, norepinephrine, serotonin) by inhibiting MAO, a mitochondrial enzyme that normally breaks down monoamines. Tyramine is an indirect sympathomimetic found in certain foods (eg, aged cheeses, cured meats, draft beer) that is usually broken down in the gastrointestinal tract by MAO. In MAO inhibitor–treated patients, tyramine escapes degradation and enters the systemic circulation, leading to a hypertensive crisis.

Due to the risks of tyramine-induced hypertensive crisis and serotonin syndrome, MAO inhibitors are typically reserved for treatment-resistant depression.

(Choice A) MAO inhibitors do not affect the binding of monoamines to their receptors. Examples of commonly used monoamine receptor blockers include dopamine receptor antagonists (eg, antipsychotics) and adrenergic receptor antagonists (eg, mirtazapine).

(Choice C) MAO inhibitors do not affect presynaptic monoamine uptake.

(Choices D, E, and F) Other classes of antidepressant medications that work by blocking presynaptic uptake are selective for 1 or 2 neurotransmitters. Selective serotonin reuptake inhibitors block presynaptic serotonin reuptake and are used first-line for depression and many anxiety disorders. Atomoxetine is a norepinephrine reuptake inhibitor used in attention-deficit hyperactivity disorder. Dual reuptake inhibitors include tricyclic antidepressants, which inhibit serotonin and norepinephrine reuptake, and bupropion, a norepinephrine-dopamine reuptake inhibitor used to treat depression and tobacco dependence.

Educational objective:
Monoamine oxidase (MAO) is a mitochondrial enzyme that breaks down monoamine neurotransmitters (eg, dopamine, norepinephrine, serotonin). Tyramine-induced hypertensive crisis can occur in patients taking MAO inhibitors who consume foods containing high amounts of tyramine (eg, aged cheeses, cured meats, draft beer).

References

- Current place of monoamine oxidase inhibitors in the treatment of depression.

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Educational objective:
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References

- Current place of monoamine oxidase inhibitors in the treatment of depression.
- Dietary restrictions and drug interactions with monoamine oxidase inhibitors: an update.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Monoamine oxidase inhibitors
Subject	System	Topic

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A 20-year-old college student comes to the office due to falling asleep at inappropriate times. He has an irresistible urge to sleep during the day, and these "naps" occur unpredictably, sometimes at the start of class or during examinations. He sleeps 6-7 hours per night and feels refreshed when he awakens. He also experiences frightening auditory hallucinations before falling asleep. He was recently in a motor vehicle collision after falling asleep at the wheel, which resulted in only a minor sprain of his wrist. He does not use tobacco, alcohol, or illicit drugs. Physical examination is unremarkable. Which of the following is the best treatment for this patient's condition?

A. Carbamazepine
B. Clonazepam
C. Melatonin
D. Modafinil
E. Zolpidem

Submit

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- A. Carbamazepine (6%)
- B. Clonazepam (5%)
- C. Melatonin (6%)
- ✓ D. Modafinil (74%)
- E. Zolpidem (7%)

Omitted
Correct answer
D

74%
Answered correctly

02 secs
Time Spent

01/18/2020
Last Updated

Explanation

Narcolepsy	
DSM-5 diagnostic criteria	• Recurrent lapses into sleep or naps (≥3 times/week for 3 months) • ≥1 of the following: ◦ Cataplexy: Brief loss of muscle tone precipitated by strong emotion (eg, laughter, excitement)

Narcolepsy	

DSM-5 diagnostic criteria	• Recurrent lapses into sleep or naps (≥3 times/week for 3 months)
	• ≥1 of the following:
	  ◦ Cataplexy: Brief loss of muscle tone precipitated by strong emotion (eg, laughter, excitement)
	  ◦ Low cerebrospinal fluid levels of hypocretin-1
	  ◦ Shortened REM sleep latency

Associated features	• Hypnagogic or hypnopompic hallucinations • Sleep paralysis

Narcolepsy is a rare neurologic disorder characterized by episodes of irresistible sleep during the day and usually one or more REM sleep–related phenomena such as **cataplexy** (ie, sudden weakness triggered by strong emotions), **hypnagogic/hypnopompic hallucinations** (ie, hallucinations while falling asleep or awakening, respectively), and **sleep paralysis** (ie, physiologic sleep paralysis that persists on awakening/falling asleep). The etiology of narcolepsy is believed to be due to low levels of the stimulatory neurotransmitter orexin (ie, hypocretin), which is involved in maintaining wakefulness and suppressing REM sleep–related phenomena.

Treatment involves the use of agents that promote wakefulness (psychostimulants). **Modafinil**, a nonamphetamine stimulant, has become the first-line agent because it is effective and well tolerated and its misuse is rare. The mechanism of action is not well described, but modafinil may enhance dopaminergic signaling. Amphetamines are second-line agents due to their sympathomimetic side effects (eg, hypertension, arrhythmia, psychosis) and risk for misuse and dependency.

(Choice A) Carbamazepine is used to treat seizures, bipolar disorder, and trigeminal neuralgia, not narcolepsy.

(Choices B and E) Zolpidem is a nonbenzodiazepine hypnotic used for insomnia. The use of zolpidem or a benzodiazepine (eg, clonazepam) in patients with narcolepsy is relatively contraindicated due to the risk of worsening daytime sedation.

(Choice C) Melatonin is used for treating jet lag and delayed sleep-wake phase syndrome, not narcolepsy.

Educational objective:
Treatment for narcolepsy includes psychostimulants (eg, modafinil) for daytime sleepiness.

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	• Sleep paralysis

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Educational objective:
Treatment for narcolepsy includes psychostimulants (eg, modafinil) for daytime sleepiness.

References

- Treatment options for narcolepsy.
- Management of narcolepsy.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Narcolepsy
Subject	System	Topic

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A 76-year-old man comes to the office due to severe insomnia of several months' duration. He has trouble falling asleep and feels tired and irritable during the day. The patient's other medical problems include hypertension and a prior cerebrovascular accident with residual right leg weakness. He takes aspirin, rosuvastatin, and lisinopril regularly as prescribed. Temperature is 36.7 C (98.1 F), blood pressure is 118/76 mm Hg, pulse is 62/min, and respirations are 14/min. Examination shows clear lungs with normal S1 and S2. The abdomen is soft and nontender. In addition to nonpharmacologic interventions for insomnia, short-term pharmacologic therapy is being considered. Which of the following medications has the lowest risk of causing adverse effects in this patient?

A. Alprazolam
B. Amitriptyline
C. Clonazepam
D. Diazepam
E. Diphenhydramine
F. Quetiapine
G. Ramelteon

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A. Alprazolam (8%)
B. Amitriptyline (1%)
C. Clonazepam (2%)
D. Diazepam (3%)
E. Diphenhydramine (9%)
F. Quetiapine (3%)
✓ G. Ramelteon (71%)

Omitted
Correct answer
G

71%
Answered correctly

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Explanation

Insomnia is common in the elderly population and can significantly impair quality of life. Nonpharmacologic interventions such as sleep hygiene

Insomnia is common in the elderly population and can significantly impair quality of life. Nonpharmacologic interventions such as sleep hygiene measures and cognitive-behavioral therapy are recommended for initial management. When nonpharmacologic interventions fail, **pharmacotherapy** may be indicated but must be used with extreme **caution in elderly patients** and should generally be limited to short-term management. Medication selection for elderly patients requires special attention to safety issues due to this population's increased sensitivity to adverse effects of medications in general and sedative-hypnotic agents in particular (eg, oversedation, dizziness, confusion, impaired psychomotor performance, ataxia).

Of the currently available sedative-hypnotic agents, the melatonin agonist **ramelteon** has demonstrated the **lowest side-effect burden** in older adults. Ramelteon binds with high affinity to melatonin receptors in the suprachiasmatic nucleus.

(Choices A, C, and D) Benzodiazepines should be avoided in elderly patients due to the increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents when taking these medications.

(Choices B and E) Amitriptyline, a tricyclic antidepressant, and diphenhydramine, an antihistamine, should be avoided in the elderly due to their strong anticholinergic effects and risks of sedation, delirium, and falls.

(Choice F) Quetiapine is a second-generation antipsychotic that would not be appropriate as a first-line treatment for insomnia. Antipsychotics carry a risk of increased falls and cardiac mortality in older adults and should not be used without an appropriate indication (eg, psychosis, dangerous agitation).

Educational objective:
Benzodiazepines, antihistamines, and sedating antidepressants should be avoided in the treatment of insomnia in elderly patients due to their adverse effects. Ramelteon, a melatonin agonist, has a lower side-effect burden than other sedative-hypnotic agents and is effective in reducing time to sleep onset in the elderly.

References

- Review of safety and efficacy of sleep medicines in older adults.
- American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults.

Pharmacology Psychiatric/Behavioral & Substance Abuse Insomnia

Insomnia is common in the elderly population and can significantly impair quality of life. Nonpharmacologic interventions such as sleep hygiene measures and cognitive-behavioral therapy are recommended for initial management. When nonpharmacologic interventions fail, **pharmacotherapy** may b

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Educational objective:

Benzodiazepines, antihist

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References

- Review of safety and
- American Geriatrics S

Exhibit Display

Side effects of commonly used drugs in the elderly	
Digoxin	• Arrythmias • Nausea & vomiting • Confusion & weakness
Benzodiazepines	• Delirium, falls, fractures
1st-generation antihistamines & tricyclic antidepressants	• Cognitive decline, delirium, hallucination • Orthostatic hypotension, falls • Urinary retention, constipation
Opioid analgesics	• Constipation • Sedation, confusion, falls
Antipsychotics	• ↑ Stroke & mortality in dementia patients
Long-acting sulfonylureas	• Hypoglycemia
Fluoroquinolones	• Tendon inflammation & rupture

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Pharmacology Psychiatric/Behavioral & Substance Abuse Insomnia

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A 25-year-old man is brought to the emergency department due to severe agitation and aggressive behavior. He speaks loudly and rapidly, stating that he has "superpowers" of mind control and that violence is the only way to defend against "the conspiracy." The patient has a history of bipolar disorder and is prescribed olanzapine, lithium, and fluoxetine, although it is unclear if he has been compliant. The patient requires several doses of medication in the emergency department to calm down and is subsequently admitted to the hospital for further psychiatric evaluation. The following night he is found lying very still on his bed and does not respond to questions. Temperature is 40.6 C (105.1 F), blood pressure is 157/90 mm Hg, pulse is 102/min, and respirations are 20/min. Examination is significant for diaphoresis and diffuse rigidity in upper and lower extremities. Which of the following is the most likely explanation for this patient's current symptoms?

A. Acute dystonic reaction
B. Akathisia
C. Drug-induced parkinsonism
D. Lithium toxicity
E. Neuroleptic malignant syndrome
F. Serotonin syndrome

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A. Acute dystonic reaction (5%)
B. Akathisia (1%)
C. Drug-induced parkinsonism (2%)
D. Lithium toxicity (2%)
✓ E. Neuroleptic malignant syndrome (78%)
F. Serotonin syndrome (10%)

Omitted
Correct answer
E

78%
Answered correctly

02 secs
Time Spent

02/17/2020
Last Updated

Explanation

	Neuroleptic malignant syndrome	Serotonin syndrome

	Neuroleptic malignant syndrome	Serotonin syndrome
Precipitant	• Dopamine antagonist	• Serotonergic agent
Onset	• 1-3 days	• <1 day
Overlapping features	• Altered mental status • Sympathetic hyperactivity (eg, hyperthermia, hypertension, tachycardia, diaphoresis)	• Altered mental status • Sympathetic hyperactivity (eg, hyperthermia, hypertension, tachycardia, diaphoresis)
Distinct features	• Diffuse rigidity ("lead-pipe") • Hyporeflexia	• Clonus • Hyperreflexia

This patient is experiencing a manic episode with psychotic features and most likely received multiple doses of antipsychotic medication to control his agitation in the emergency department. His **hyperthermia**, **sympathetic hyperactivity** (eg, diaphoresis, tachycardia), severe **muscle rigidity** (frequently described as "lead-pipe rigidity"), and **altered mental status** are characteristic of **neuroleptic malignant syndrome (NMS)**.

NMS is a potentially life-threatening adverse reaction to **antipsychotics** (ie, neuroleptics) that typically presents 1-3 days after initiation or dose escalation. It is thought to be caused by antagonism of central dopaminergic systems involved in thermoregulation and regulation of muscle tone and movement. Treatment involves cessation of the causative agent; benzodiazepines and **dantrolene** (a postsynaptic muscle relaxant) are used for treating severe cases.

(Choices A, B, and C) Antipsychotic D2 dopamine receptor antagonism in the nigrostriatal pathway can cause a variety of reactions (known as extrapyramidal symptoms) that can be confused with NMS. Acute dystonic reactions involve distressing contractions of the neck, mouth, and tongue. Akathisia is a subjective feeling of intense restlessness and an inability to sit still. Drug-induced parkinsonism manifests as rigidity, bradykinesia, and tremor. None of these conditions involves altered mental status, hyperthermia, or sympathetic hyperactivity.

(Choice D) Lithium is a mood stabilizer used in bipolar disorder but is not used to control acute agitation and psychosis. Acute lithium toxicity typically begins with nausea, vomiting, and diarrhea, with neuromuscular signs developing later.

(Choice F) Although serotonin syndrome (due to overdose or combinations of serotonergic drugs) can also present with mental status changes,

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NMS is a potentially life-threatening adverse reaction to **antipsychotics** (ie, neuroleptics) that typically presents 1-3 days after initiation or dose escalation. It is thought to be caused by antagonism of central dopaminergic systems involved in thermoregulation and regulation of muscle tone and movement. Treatment involves cessation of the causative agent; benzodiazepines and **dantrolene** (a postsynaptic muscle relaxant) are used for treating severe cases.

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(Choice F) Although serotonin syndrome (due to overdose or combinations of serotonergic drugs) can also present with mental status changes, hyperthermia, and sympathetic hyperactivity, it typically presents with neuromuscular hyperactivity (eg, clonus, hyperreflexia) as opposed to the diffuse rigidity seen in NMS and in this patient.

Educational objective:
Neuroleptic malignant syndrome (NMS) is an adverse reaction to antipsychotic medication characterized by severe "lead-pipe" rigidity, hyperthermia, sympathetic hyperactivity, and mental status changes. NMS is characterized by severe rigidity rather than the neuromuscular irritability (eg, hyperreflexia, myoclonus) seen in serotonin syndrome.

References

- Neuroleptic malignant syndrome: a review from a clinically oriented perspective.
- Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Neuroleptic malignant syndrome
Subject	System	Topic

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A 60-year-old man is found by his daughter to be confused at home. Emergency medical services are called and he is brought to the emergency department by ambulance. The patient's daughter, who accompanies him, says that she found an empty bottle of amitriptyline next to his bed. He has not been taking any other medications. In the emergency department, the patient is delirious and says that he sees small animals running around in the corner of the room. He appears flushed. The patient has a brief seizure and becomes unconscious. Temperature is 37.2 C (99 F), blood pressure is 90/62 mm Hg, and pulse is 120/min. Both pupils are dilated and equally reactive to light, and his skin and mucous membranes are dry. Initial ECG shows QRS widening and QTc prolongation. He is transferred to the intensive care unit but dies despite resuscitation attempts. Which of the following pharmacological effects most likely contributed to the patient's death?

A. Increased antihistamine effect

B. Sodium channel inhibition

C. Synaptic norepinephrine accumulation

D. Synaptic serotonin accumulation

E. Uncontrolled presynaptic dopamine release

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- A. Increased antihistamine effect (4%)
- ✓ B. Sodium channel inhibition (66%)
- C. Synaptic norepinephrine accumulation (11%)
- D. Synaptic serotonin accumulation (16%)
- E. Uncontrolled presynaptic dopamine release (2%)

Omitted
Correct answer
B

66%
Answered correctly

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Explanation

Tricyclic antidepressant pharmacology	
Inhibitory effects	Consequences

Tricyclic antidepressant pharmacology	
Inhibitory effects	**Consequences**
Central & peripheral muscarinic acetylcholine receptors	Tachycardia, delirium, dilated pupils, flushing, decreased sweating, hyperthermia, ileus, urinary retention
Peripheral alpha-1 adrenergic receptors	Peripheral vasodilation (orthostatic hypotension)
Cardiac fast sodium channels	Conduction defects, arrhythmias
Presynaptic (NE & 5-HT) neurotransmitter reuptake	Antidepressant & anxiolytic effects, seizures, tremors
Histamine (H1) receptors	Sedation, increased appetite

Tricyclic antidepressants (TCAs), such as amitriptyline, inhibit the reuptake of norepinephrine and serotonin and are used in the treatment of depression. They also **inhibit** fast **sodium channel conduction**, slowing down myocardial depolarization and potentially leading to **cardiac arrhythmias** in overdose. **Refractory hypotension** results from decreased cardiac contractility and direct peripheral vasodilation (from peripheral alpha-1 adrenergic receptor antagonism). Most deaths from **TCA overdose** are due to cardiac arrhythmias and refractory hypotension.

Treatment of TCA overdose involves **sodium bicarbonate** ($NaHCO_3$) therapy. $NaHCO_3$ increases serum pH, promoting TCA dissociation from sodium channels, and increases extracellular sodium concentration. These effects help overcome the sodium channel blockade induced by TCAs.

(Choice A) TCAs cause antihistaminic effects by antagonizing histamine (H1) receptors. This can cause increased sedation and appetite but is not implicated in death from TCAs.

(Choice C) TCAs block the amine reuptake pumps within the synaptic cleft, which normally terminate amine transmission. This permits a longer interaction between the neurotransmitter and the receptor, which is thought to account for TCA antidepressant properties. However, synaptic norepinephrine accumulation is not the mechanism by which death occurs following TCA overdose.

(Choice D) Serotonin syndrome must be considered in suspected antidepressant overdose. Patients with serotonin syndrome have hyperthermia, autonomic instability, hyperreflexia, myoclonus, and diaphoresis. Cardiac changes are not usually indicative of serotonin syndrome. Although symptoms of excess serotonin may be present after TCA overdose, most deaths are due to cardiac toxicity.

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(Choice E) TCAs do not increase presynaptic release of dopamine. Amphetamines increase the release of dopamine (and norepinephrine) by vesicles in presynaptic neurons.

Educational objective:
Tricyclic antidepressant overdose can cause fatal cardiac arrhythmias and refractory hypotension due to inhibition of fast sodium channels in cardiac myocytes. Sodium bicarbonate is used to treat associated cardiac toxicity and works by increasing serum pH and extracellular sodium (alleviating fast sodium channel blockade).

References

- Guidelines in Emergency Medicine Network (GEMNet): guideline for the management of tricyclic antidepressant overdose.
- The return of an old nemesis: survival after severe tricyclic antidepressant toxicity, a case report.
- Tricyclic antidepressant poisoning: cardiovascular toxicity.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Tricyclic antidepressants
Subject	System	Topic

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A 67-year-old man comes to the hospital due to an acute worsening of chronic back pain associated with new-onset bilateral leg weakness and numbness. He has a history of colorectal cancer with vertebral metastases for which he has received colectomy, chemotherapy, and radiation treatment. The patient takes oral morphine sulfate for his back pain. Examination shows focal vertebral tenderness, along with reduced muscular strength, decreased sensitivity to light touch, and spasticity in both legs. Imaging studies reveal a vertebral compression fracture with cord compression. Surgical decompression is planned. Which of the following drugs may precipitate opioid withdrawal symptoms if used in this patient?

- A. Buprenorphine
- B. Codeine
- C. Fentanyl
- D. Hydromorphone
- E. Meperidine
- F. Methadone
- G. Oxymorphone

Submit

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- ✓ A. Buprenorphine (45%)
- B. Codeine (5%)
- C. Fentanyl (11%)
- D. Hydromorphone (3%)
- E. Meperidine (12%)
- F. Methadone (18%)
- G. Oxymorphone (2%)

Omitted
Correct answer
A

45%
Answered correctly

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Explanation

Opioids work by selectively binding to G protein-coupled opioid receptors, mimicking the actions of endogenous opioid peptides. However, long-

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Omitted
Correct answer
A

45%
Answered correctly

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Last Updated

Explanation

Opioids work by selectively binding to G protein-coupled opioid receptors, mimicking the actions of endogenous opioid peptides. However, long-term activation of mu-opioid receptors on nociception-transmitting neurons is associated with increased pain sensitivity (central sensitization) due to:

Opioids work by selectively binding to G protein-coupled opioid receptors, mimicking the actions of endogenous opioid peptides. However, long-term activation of mu-opioid receptors on nociception-transmitting neurons is associated with increased pain sensitivity (central sensitization) due to:

- Increased turnover of inhibitory opioid receptors (receptor downregulation) and decoupling of receptors from their second messenger system (receptor decoupling)
- Upregulation of excitatory N-methyl-D-aspartate (NMDA) receptors

This manifests as an increasing dose requirement to provide the same level of pain relief (**tolerance**) and pain sensations triggered by benign stimuli (**opioid-induced hyperalgesia**). Opioid withdrawal can occur within 24-48 hours of acute cessation in opioid-tolerant patients and is characterized by nausea/vomiting, myalgias, dilated pupils, diaphoresis, and tachycardia.

Buprenorphine is a partial opioid agonist that has low intrinsic activity (efficacy) for opioid mu-receptors. However, it binds with high affinity (potency) and can prevent binding of other opioid medications. Therefore, buprenorphine acts as an opioid receptor antagonist in the presence of full opioid agonists and can precipitate **withdrawal** in opioid-tolerant patients with chronic pain.

(Choices B, C, D, E, F, and G) These other agents are full agonists of the opioid mu-receptor. Although they vary in potency, none have significant opioid receptor antagonist properties. Use of these drugs in equianalgesic doses should not cause withdrawal.

Educational objective:
Buprenorphine is a partial opioid receptor agonist that binds with high affinity but has low intrinsic activity. In patients on long-term opioid therapy, buprenorphine can displace other opioids and precipitate withdrawal.

References

- Buprenorphine is a weak partial agonist that inhibits opioid receptor desensitization.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Opioids
Subject	System	Topic

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A 56-year-old man with a history of severe depression seeks a new physician after immigrating to the United States. His depression has been treated with phenelzine since diagnosis, and his new physician decides to switch him to sertraline. The patient is informed that he must wait at least 2 weeks after discontinuing phenelzine before starting the new drug. Which of the following processes occurs during this washout interval to allow sertraline therapy to be initiated safely?

A. G protein–coupled receptor internalization
B. Inositol monophosphatase inhibition
C. Monoamine oxidase inhibition
D. Monoamine receptor downregulation
E. Monoamine reuptake inhibition
F. Synthesis of monoamine oxidase

Submit

A 56-year-old man with a history of severe depression seeks a new physician after immigrating to the United States. His depression has been treated with phenelzine since diagnosis, and his new physician decides to switch him to sertraline. The patient is informed that he must wait at least 2 weeks after discontinuing phenelzine before starting the new drug. Which of the following processes occurs during this washout interval to allow sertraline therapy to be initiated safely?

- A. G protein–coupled receptor internalization (1%)
- B. Inositol monophosphatase inhibition (0%)
- C. Monoamine oxidase inhibition (6%)
- D. Monoamine receptor downregulation (24%)
- E. Monoamine reuptake inhibition (3%)
- ✓ F. Synthesis of monoamine oxidase (63%)

Omitted
Correct answer
F

63%
Answered correctly

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Last Updated

Explanation

Monoamine oxidase inhibitors

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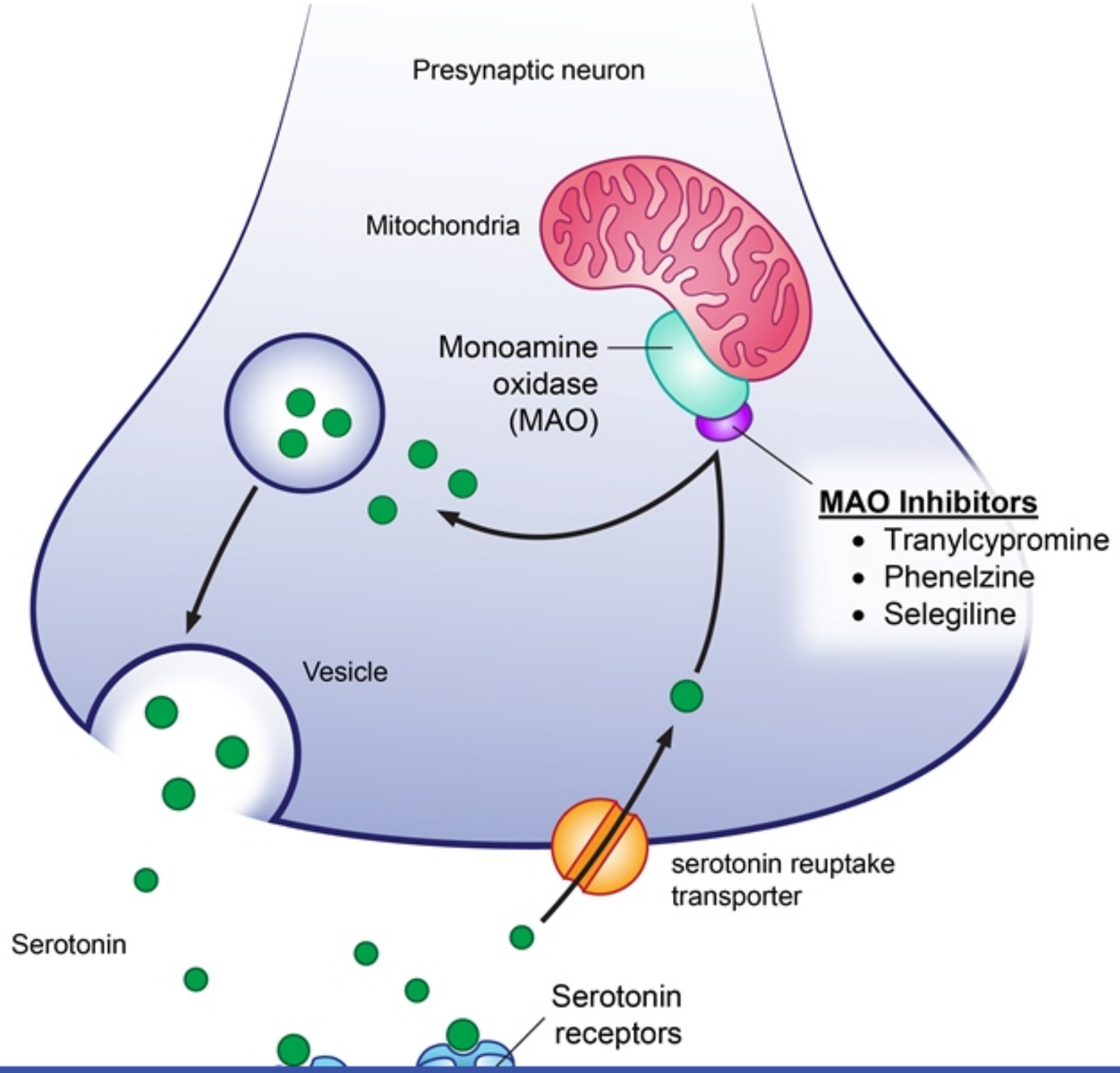
Monoamine oxidase inhibitors



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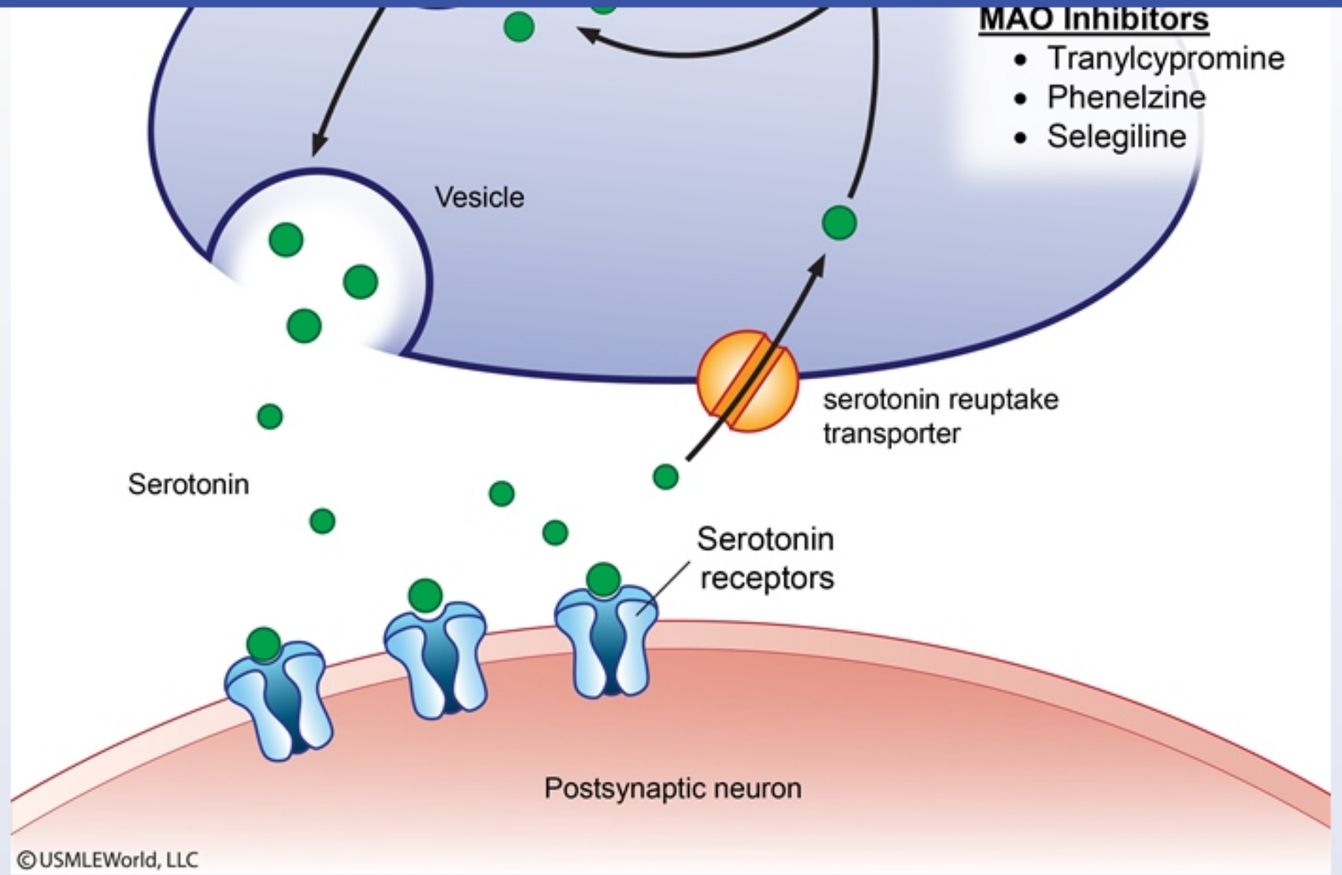

The pathophysiologic basis of depression is hypothesized to involve the dysregulation of monoamine (eg, serotonin, norepinephrine, dopamine) neurotransmission. Most antidepressant medications act by various mechanisms to increase synaptic concentrations of these neurotransmitters, particularly serotonin. Monoamine oxidase (MAO) is an enzyme located in presynaptic nerve terminals that is responsible for the breakdown of monoamine neurotransmitters. **Phenelzine**, a **monoamine oxidase inhibitor**, works by irreversibly binding and inhibiting both types of MAO: A and B. This results in increased presynaptic availability of monoamine neurotransmitters, thereby increasing their release into the synaptic cleft. Because phenelzine irreversibly inhibits MAO, it may take up to 2 weeks following discontinuation of the drug before MAO is resynthesized to a level adequate for normal monoamine degradation.

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Sertraline is a selective serotonin reuptake inhibitor (SSRI) that specifically increases synaptic serotonin levels. Coadministration of an SSRI and an MAO inhibitor is contraindicated due to the risk of **serotonin syndrome**, a potentially fatal condition characterized by altered mental status, neuromuscular excitation (eg, hyperreflexia, clonus), and autonomic hyperactivity (eg, hyperthermia, tachycardia, diaphoresis). To avoid serotonin syndrome, patients must wait at least 2 weeks after MAO inhibitor discontinuation before initiating SSRI therapy, thereby allowing sufficient time for regeneration of the MAO enzyme.

(Choice A) Monoamine (eg, serotonin) receptors are G protein–coupled receptors. Internalization of activated G protein–coupled receptors plays a role in downregulating postsynaptic signal transduction when synaptic monoamine levels are chronically increased. However, this is not the reason for the 2-week washout period from phenelzine, which is required to resynthesize the irreversibly inhibited MAO enzyme.

(Choice B) Inositol monophosphatase inhibition is hypothesized to be one of the mechanisms by which lithium exerts its antidepressant and antimanic effects. Inositol monophosphatase is not affected by MAO inhibitors.

(Choice C) MAO inhibition arrests the breakdown of monoamines, thereby increasing their release into the synaptic cleft. Overall MAO functioning gradually increases after discontinuation of irreversible MAO inhibitors (eg, tranylcypromine, phenelzine) as new MAO is synthesized.

(Choice D) Increased monoamine neurotransmission due to antidepressant treatment causes downregulation of postsynaptic monoamine (eg, serotonin) receptors, decreasing their density within the synaptic cleft. This (along with other chronic, downstream neuromodulatory changes) is responsible for the delayed clinical effects of antidepressants.

(Choice E) Presynaptic monoaminergic neurons actively take up norepinephrine, dopamine, and serotonin through reuptake transporters and repackage them into synaptic vesicles for future neurotransmission. Monoamine reuptake inhibitors, such as tricyclic antidepressants and SSRIs,

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Educational objective:
Coadministration of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors can produce excessive synaptic serotonin levels secondary to decreased reuptake and decreased degradation of serotonin, potentially causing serotonin syndrome. To avoid this risk, a 2-week washout period after discontinuing an MAO inhibitor and before initiating SSRI therapy is required to allow sufficient time for MAO regeneration.

References

- Switching and stopping antidepressants.

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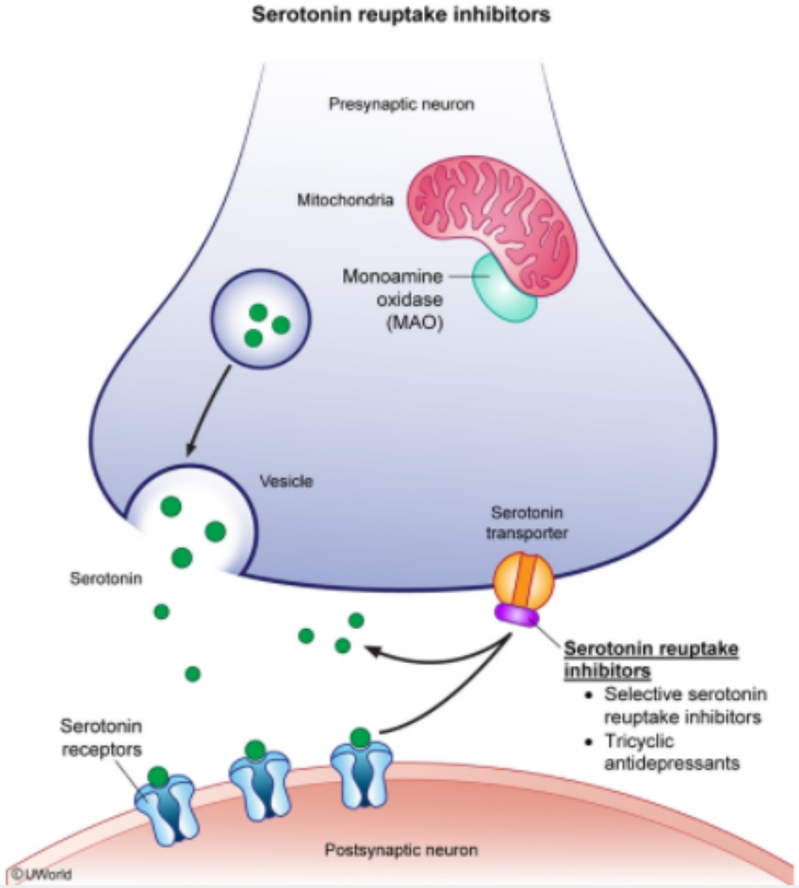

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Educational objective:
Coadministration of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors can produce excessive synaptic serotonin levels secondary to decreased reuptake and decreased degradation of serotonin, potentially causing serotonin syndrome. To avoid this risk, a 2-week washout period after discontinuing an MAO inhibitor and before initiating SSRI therapy is required to allow sufficient time for MAO regeneration.

References

- Switching and stopping antidepressants.
- Overview of serotonin syndrome.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Serotonin syndrome
Subject	System	Topic

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 32-year-old woman comes to the office because she has felt sad and worthless for the past 3 months and often cries for no obvious reason. The patient has difficulty sleeping, her appetite is decreased, and she no longer enjoys spending time with friends. She has no significant medical history. A pregnancy test is negative, and TSH is within normal limits. The physician discusses the diagnosis with the patient and initiates first-line pharmacologic treatment. Two days later, the patient is brought to the emergency department after being found lying down next to an empty bottle of the prescribed medication. Temperature is 38.9 C (102 F), blood pressure is 146/92 mm Hg, and heart rate is 118/min and regular. The patient is disoriented, tremulous, and diaphoretic. She has abdominal cramps and diarrhea. Neurologic examination reveals pupillary dilation, bilateral hyperreflexia in the lower extremities, and bilateral, inducible ankle clonus.

Item 1 of 2

Which of the following amino acids is a precursor of the neurotransmitter most likely responsible for this patient's current symptoms?

A. Glutamic acid
B. Histidine
C. Methionine
D. Tryptophan
E. Tyrosine

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Item 1 of 2

Which of the following amino acids is a precursor of the neurotransmitter most likely responsible for this patient's current symptoms?

A. Glutamic acid (5%)
B. Histidine (1%)
C. Methionine (1%)
✓ D. Tryptophan (65%)
E. Tyrosine (24%)

Omitted
Correct answer
D

65%
Answered correctly

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Serotonin syndrome	
Causes	• Serotonergic medications, especially in combination (eg, SSRI/SNRI, TCA, tramadol) • Drug interactions: Serotonergic medication & MAOI or linezolid • Intentional overdose of serotonergic medications • Serotonergic drugs of abuse (eg, MDMA)
Clinical features	• Mental status changes (eg, anxiety, agitation, delirium) • Autonomic dysregulation (eg, diaphoresis, hypertension, tachycardia, hyperthermia, vomiting, diarrhea) • Neuromuscular hyperactivity (eg, tremor, myoclonus, hyperreflexia)
Management	• Discontinuation of all serotonergic medications • Supportive care, sedation with benzodiazepines • Serotonin antagonist (cyproheptadine) if supportive measures fail

MAOI = monoamine oxidase inhibitor; **MDMA** = 3,4-methylenedioxymethamphetamine; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant.

This patient's feelings of sadness and worthlessness—combined with her impaired sleep, decreased appetite, and decreased enjoyment of previously pleasurable activities (eg, socializing with friends)—lasting ≥2 weeks are consistent with major depressive disorder (MDD). First-line pharmacotherapy for MDD is a selective serotonin reuptake inhibitor (SSRI). Her apparent overdose on the prescribed SSRI and her resultant **altered mental status** (eg, disorientation), **autonomic hyperactivity** (eg, hyperthermia, tachycardia, diaphoresis), and **neuromuscular excitation** (eg, hyperreflexia, clonus, tremor) are characteristic of **serotonin syndrome**.

Serotonin syndrome is caused by excessive serotonin activity, most commonly brought on by combining SSRIs with another serotonergic agent such as a monoamine oxidase inhibitor. It may also occur with a single agent if taken in overdose. **Tryptophan** is a precursor of **serotonin**, whose biosynthesis occurs via the enzymes tryptophan hydroxylase and amino acid decarboxylase.

(Choice A) Glutamic acid is a precursor for the inhibitory neurotransmitter GABA.

MAOI = monoamine oxidase inhibitor; MDMA = 3,4-methylenedioxymethamphetamine; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

This patient's feelings of sadness and worthlessness—combined with her impaired sleep, decreased appetite, and decreased enjoyment of previously pleasurable activities (eg, socializing with friends)—lasting ≥2 weeks are consistent with major depressive disorder (MDD). First-line pharmacotherapy for MDD is a selective serotonin reuptake inhibitor (SSRI). Her apparent overdose on the prescribed SSRI and her resultant **altered mental status** (eg, disorientation), **autonomic hyperactivity** (eg, hyperthermia, tachycardia, diaphoresis), and **neuromuscular excitation** (eg, hyperreflexia, clonus, tremor) are characteristic of **serotonin syndrome**.

Serotonin syndrome is caused by excessive serotonin activity, most commonly brought on by combining SSRIs with another serotonergic agent such as a monoamine oxidase inhibitor. It may also occur with a single agent if taken in overdose. **Tryptophan** is a precursor of **serotonin**, whose biosynthesis occurs via the enzymes tryptophan hydroxylase and amino acid decarboxylase.

(Choice A) Glutamic acid is a precursor for the inhibitory neurotransmitter GABA.

(Choice B) Histidine is the precursor of histamine, which plays a role in allergic (atopic) reactions.

(Choice C) Methionine is a precursor or intermediate in the synthesis of cysteine, carnitine, taurine, and lecithin.

(Choice E) Tyrosine is a precursor for thyroxine, dopamine, epinephrine, norepinephrine, and melanin.

Educational objective:
Serotonin syndrome is characterized by altered mental status, autonomic hyperactivity, and neuromuscular excitation (eg, hyperreflexia, clonus). Causes include high doses and/or combinations of serotonergic drugs (eg, SSRI and MAOI). Tryptophan is a precursor for serotonin.

References

- Conundrums in neurology: diagnosing serotonin syndrome - a meta-analysis of cases.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Selective serotonin reuptake inhibitors
Subject	System	Topic

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Item 2 of 2

The patient is admitted to the hospital and supportive therapy is initiated. However, she remains disoriented with only limited improvement of her condition. Which of the following is the antidote for this patient's condition?

A. Cyproheptadine

B. Flumazenil

C. Haloperidol

D. Naloxone

E. Propranolol

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Item 2 of 2

The patient is admitted to the hospital and supportive therapy is initiated. However, she remains disoriented with only limited improvement of her condition. Which of the following is the antidote for this patient's condition?

- ✓ A. Cyproheptadine (74%)
- B. Flumazenil (11%)
- C. Haloperidol (2%)
- D. Naloxone (4%)
- E. Propranolol (6%)

Omitted
Correct answer
A

74%
Answered correctly

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Explanation

Serotonin syndrome is characterized by altered mental status, autonomic hyperactivity, and neuromuscular excitation, which occur as a result of excessive serotonin activity in the CNS. Treatment includes supportive care, including airway and temperature maintenance as well as hydration. When supportive measures fail, **cyproheptadine** can be given as an **antidote** as it functions as a **serotonin antagonist**. Cyproheptadine is a first-generation antihistamine with nonspecific 5-HT1 and 5-HT2 receptor antagonistic properties.

(Choice B) Flumazenil is the antidote for benzodiazepine overdose, not serotonin syndrome.

(Choice C) Haloperidol is an antidopaminergic agent used primarily for the treatment of psychosis.

A

Answered correctly Time Spent Last Updated

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(Choice B) Flumazenil is the antidote for benzodiazepine overdose, not serotonin syndrome.

(Choice C) Haloperidol is an antidopaminergic agent used primarily for the treatment of psychosis.

(Choice D) Naloxone is the antidote for narcotic overdose.

(Choice E) Short-acting antihypertensives, such as esmolol or nitroprusside, can be used to treat hypertension associated with serotonin syndrome. Antihypertensive agents with longer half-lives, such as propranolol, should be avoided due to the risk of developing hypotension and shock.

Educational objective:
Cyproheptadine is an antihistamine with antiserotonergic properties that can be used as an antidote in severe cases of serotonin syndrome that do not respond to supportive measures.

References

- Mild serotonin syndrome: a report of 12 cases.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Selective serotonin reuptake inhibitors
Subject	System	Topic

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A 45-year-old woman with a history of opioid use disorder and HIV infection is brought to the emergency department due to worsening lethargy. The patient receives methadone maintenance therapy, which she recently restarted after being hospitalized for an HIV-related infection. Her infection improved after inpatient treatment, and she continues to take appropriate antimicrobials as an outpatient. Her current temperature is 37 C (98.6 F), blood pressure is 116/68 mm Hg, pulse is 90/min, and respirations are 10/min. On physical examination, the patient is somnolent and withdraws all extremities to painful stimuli. The pupils are small and sluggish to react. Brain imaging reveals no new findings, and renal function tests are within normal limits. Use of which of the following medications most likely contributed to this patient's current condition?

A. Atovaquone
B. Dapsone
C. Fluconazole
D. Rifampin
E. Valganciclovir

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A. Atovaquone (4%)
B. Dapsone (11%)
✓ C. Fluconazole (54%)
D. Rifampin (20%)
E. Valganciclovir (9%)

Omitted
Correct answer
C

54%
Answered correctly

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Time Spent

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Explanation

Common medications that increase methadone effect
• Fluconazole, voriconazole, ketoconazole • Ciprofloxacin, clarithromycin

Explanation

Common medications that increase methadone effect
• Fluconazole, voriconazole, ketoconazole • Ciprofloxacin, clarithromycin • Cimetidine • Fluvoxamine

Methadone is a **mu-opioid receptor agonist** used for maintenance treatment of opioid use disorder. It has a long half-life, which allows it to effectively suppress cravings and withdrawal symptoms. Like all opioid medications, methadone carries a risk of **overdose**, which is characterized by somnolence, miosis, and respiratory depression (ie, bradypnea). Another side effect is QTc prolongation, which can predispose to torsade de pointes.

Methadone is **extensively metabolized** by the cytochrome P-450 system, particularly by **CYP3A4**. In this case, the patient likely received **fluconazole**, an antifungal medication that is used in the treatment of **cryptococcal meningitis** (which typically occurs in patients with a CD4 count <100 cells/μL). Fluconazole **inhibits** CYP3A4, which can **increase** plasma **methadone concentration** and lead to opioid toxicity. Interestingly, not all P-450 3A4 inhibitors prolong methadone effects; other medications known to cause similar interactions with methadone include voriconazole, ketoconazole, ciprofloxacin, clarithromycin, cimetidine, and fluvoxamine.

(Choices A and B) Atovaquone and dapsone are alternative agents used to prevent pneumocystis pneumonia in patients with trimethoprim-sulfamethoxazole allergy. Common side effects of dapsone include hemolytic anemia and methemoglobinemia, particularly in patients with glucose-6-phosphate dehydrogenase deficiency. Neither medication has significant interactions with methadone.

(Choice D) Rifampin is used (in combination with other antibiotics) in the treatment of multiple mycobacterial infections (eg, tuberculosis, mycobacterium avium complex). It is a cytochrome P-450 inducer and can result in lower plasma concentrations of methadone, thereby decreasing its effects.

(Choice E) Valganciclovir is used for treatment and secondary prophylaxis of cytomegalovirus retinitis. Side effects include bone marrow suppression and diarrhea. It does not interact with methadone.

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(Choice E) Valganciclovir is used for treatment and secondary prophylaxis of cytomegalovirus retinitis. Side effects include bone marrow suppression and diarrhea. It does not interact with methadone.

Educational objective:
Methadone is a mu-opioid receptor agonist used for maintenance treatment for opioid use disorder; it is metabolized by the cytochrome P-450 system, particularly by CYP3A4. Certain inhibitors of CYP3A4 (eg, azoles, fluvoxamine, ciprofloxacin, clarithromycin, cimetidine) can increase plasma methadone concentration and lead to opioid toxicity (eg, sedation, respiratory depression, miosis).

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Opioids
Subject	System	Topic

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A 25-year-old graduate student comes to the office for evaluation of anxiety. She describes episodes of sudden-onset palpitations, shortness of breath, and diaphoresis during which she wants to "run away before anyone notices." The patient arrives early for her classes to get a seat close to the door and has left during lectures due to feeling "out of control." There are no specific triggers for these events, but she is worried about having another episode next week during her final examinations. She does not drink alcohol or use illicit drugs. Physical examination, ECG, and laboratory evaluation are normal. The patient is diagnosed with panic disorder. After discussion of treatment options, she decides to pursue cognitive-behavioral therapy and start a short-term anxiolytic medication that also has muscle-relaxant and anticonvulsant properties. Which of the following best describes the mechanism of action of this medication?

A. Antagonism at GABA A benzodiazepine receptor sites

B. Increased duration of chloride channel opening

C. Increased frequency of chloride channel opening

D. Inhibition of serotonin and norepinephrine reuptake

E. Inhibition of serotonin reuptake

Submit

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- A. Antagonism at GABA A benzodiazepine receptor sites (8%)
- B. Increased duration of chloride channel opening (18%)
- ✓ C. Increased frequency of chloride channel opening (67%)
- D. Inhibition of serotonin and norepinephrine reuptake (3%)
- E. Inhibition of serotonin reuptake (2%)

Omitted
Correct answer
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06/29/2020
Last Updated

Explanation

GABA A receptor

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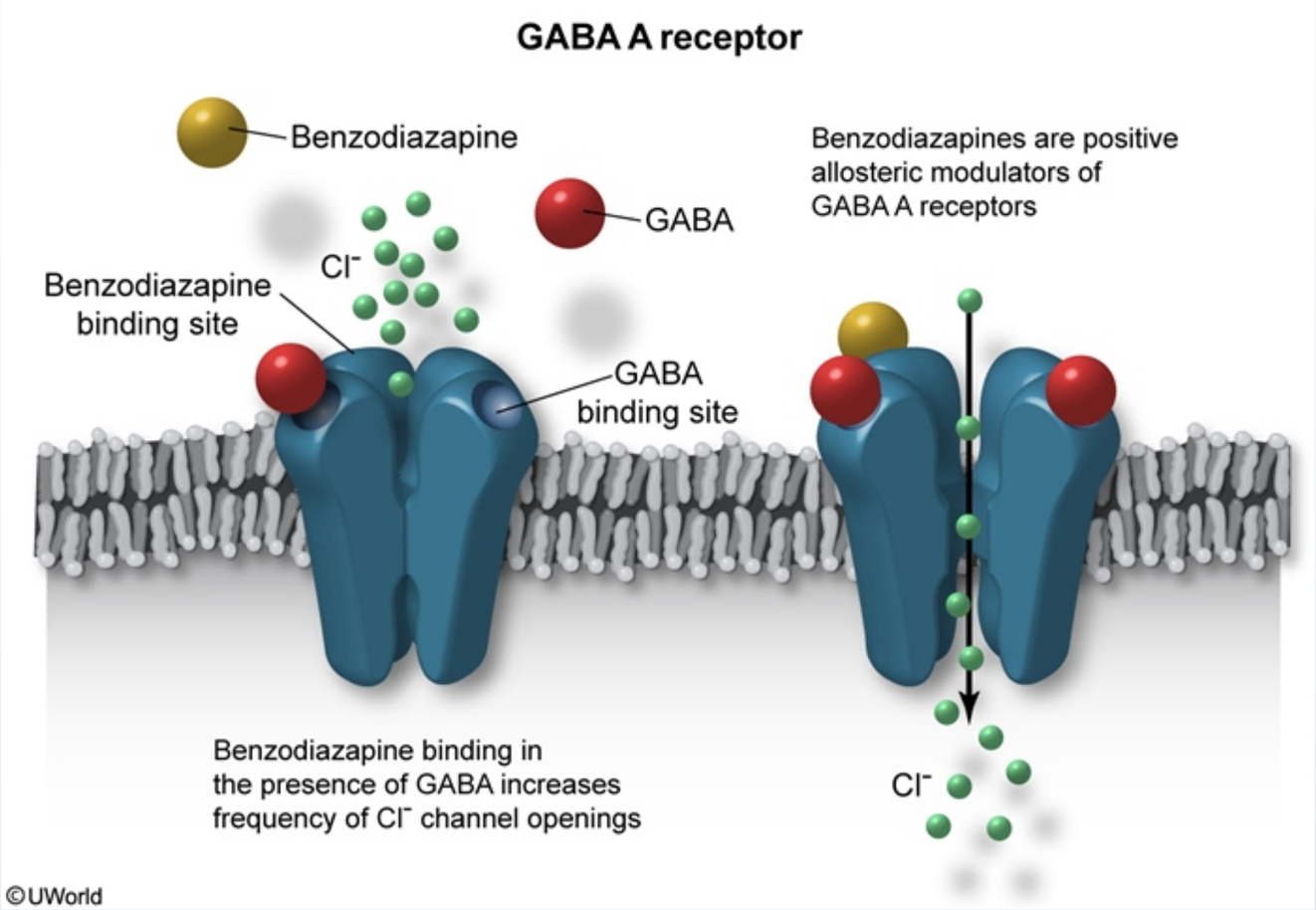

Benzodiazepines (eg, clonazepam, lorazepam) bind and modulate **$GABA_A$ receptors** on CNS neurons, resulting in an **increased frequency** of **chloride channel opening** in the presence of GABA. This increase in chloride permeability hyperpolarizes and stabilizes the membrane, rendering it less excitable, resulting in the anxiolytic, muscle-relaxant, and anticonvulsant properties of benzodiazepines. Due to risk for dependence, benzodiazepines are generally prescribed for short-term use in anxiety disorders and alcohol withdrawal syndrome.

(Choice A) Flumazenil is an antagonist at benzodiazepine receptor sites on GABA A receptors and is a reversal agent for benzodiazepine overdose.

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Benzodiazepines (eg, clonazepam, lorazepam) bind and modulate **$GABA_A$ receptors** on CNS neurons, resulting in an **increased frequency** of **chloride channel opening** in the presence of GABA. This increase in chloride permeability hyperpolarizes and stabilizes the membrane, rendering it less excitable, resulting in the anxiolytic, muscle-relaxant, and anticonvulsant properties of benzodiazepines. Due to risk for dependence, benzodiazepines are generally prescribed for short-term use in anxiety disorders and alcohol withdrawal syndrome.

(Choice A) Flumazenil is an antagonist at benzodiazepine receptor sites on GABA A receptors and is a reversal agent for benzodiazepine overdose.

(Choice B) Barbiturates (eg, phenobarbital) increase the duration of opening of the GABA A receptor–chloride channel in the presence of GABA. Although barbiturates have anxiolytic properties, they are not indicated for the treatment of anxiety disorders because of their potential to induce fatal respiratory depression.

(Choices D and E) Inhibition of serotonin reuptake is the mechanism of action of selective serotonin reuptake inhibitors (eg, fluoxetine). Inhibition of serotonin and norepinephrine reuptake is the mechanism of tricyclic antidepressants (eg, amitriptyline) and serotonin–norepinephrine reuptake inhibitors (eg, venlafaxine). These antidepressants are frequently used to treat panic disorder, but they take several weeks for symptom improvement. Unlike benzodiazepines, they do not have muscle relaxant or anticonvulsant properties.

Educational objective:
Benzodiazepines bind GABA A receptors, resulting in an increased frequency of chloride channel opening in the presence of GABA. Indications for prescribing include short-term treatment of anxiety disorders and alcohol withdrawal syndrome.

References

- Benzodiazepines I: upping the care on downers: the evidence of risks, benefits and alternatives.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Benzodiazepines
Subject	System	Topic

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A 22-year-old man is brought to the office by his mother due to a change in behavior over the past year. Nine months ago, the patient abruptly decided to quit college in his last year and insisted on moving back home to "work on my research without being disturbed." Since then, he has stopped going out with friends, seems uninterested in his usual hobbies of playing and watching football, and spends hours on his computer researching government cover-ups. He stays up late at night, sleeps during the day, and showers only once a week. The patient has no motivation to look for work; his mother reports that when she encourages him to go back to school or work, he becomes agitated and starts accusing her of "being one of the black suits." Physical examination shows poor hygiene but is otherwise normal. Laboratory evaluation, including urine drug screen, is unremarkable. A medication with which of the following primary mechanisms of action is most appropriate for this patient's condition?

- A. Alpha receptor agonism
- B. Dopamine receptor antagonism
- C. Dopamine reuptake inhibition
- D. Gamma-aminobutyric acid receptor agonism
- E. Histamine receptor antagonism
- F. Norepinephrine reuptake inhibition
- G. Serotonin reuptake inhibition

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- A. Alpha receptor agonism (0%)
- ✓ B. Dopamine receptor antagonism (76%)
- C. Dopamine reuptake inhibition (5%)
- D. Gamma-aminobutyric acid receptor agonism (2%)
- E. Histamine receptor antagonism (0%)
- F. Norepinephrine reuptake inhibition (0%)
- G. Serotonin reuptake inhibition (14%)

Omitted
Correct answer
B

76%
Answered correctly

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02/19/2020
Last Updated

Explanation

Explanation

Schizophrenia	
Diagnosis	• ≥2 of the following (at least 1 symptom from 1-3) 1. Delusions 2. Hallucinations 3. Disorganized speech 4. Disorganized or catatonic behavior 5. Negative symptoms (eg, apathy, flat affect) • Continuous impairment ≥6 months • Significant functional decline
Treatment	• Antipsychotic medication • Adjunctive psychosocial interventions (eg, social skills training, cognitive-behavioral therapy, family intervention)

This patient's paranoid delusions and negative symptoms (eg, loss of motivation, social withdrawal, decreased attention to personal hygiene) lasting >6 months are consistent with **schizophrenia**, a psychotic disorder with typical onset in early adulthood. Progressive functional impairment is common, as illustrated by this patient's academic and occupational dysfunction.

Antipsychotic medications are first-line pharmacotherapy for schizophrenia. The primary mechanism of action of antipsychotics is **antagonism** at **postsynaptic dopamine D2 receptors**. Second-generation antipsychotics (SGAs) have the additional property of serotonin type 2 receptor antagonism, and some SGAs (eg, aripiprazole) also act as D2 receptor partial agonists.

(Choice A) Alpha receptor agonism is the mechanism of action of a variety of medications (eg, vasopressors, nasal decongestants), but it does not play a role in the therapeutic action of antipsychotics.

(Choices C and F) Dopamine reuptake inhibition, usually in combination with norepinephrine reuptake inhibition, is the mechanism of action of medications used in the treatment of ADHD (eg, methylphenidate, bupropion).

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(Choices C and F) Dopamine reuptake inhibition, usually in combination with norepinephrine reuptake inhibition, is the mechanism of action of medications used in the treatment of ADHD (eg, methylphenidate, bupropion).

(Choice D) Gamma-aminobutyric acid receptor agonism is the mechanism of action of ethanol, barbiturates, benzodiazepines, and propofol.

(Choice E) Antihistamines are not a first-line treatment for schizophrenia. They are primarily used in the treatment of allergic conditions.

(Choice G) Serotonin reuptake inhibition is the mechanism of action of antidepressant medications, which are primarily used in the treatment of depressive and anxiety disorders. Although patients with schizophrenia often experience mood and anxiety symptoms, antidepressant medication would not effectively target this patient's psychotic symptoms.

Educational objective:
Antipsychotic medications are first-line pharmacotherapy for schizophrenia. Their primary mechanism of action is D2 receptor antagonism.

References

- The acute efficacy of antipsychotics in schizophrenia: a review of recent meta-analyses.
- How well do patients with a first episode of schizophrenia respond to antipsychotics: a systematic review and meta-analysis.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Psychosis
Subject	System	Topic

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A 43-year-old man comes to the office due to depression. He feels sad and unmotivated, sleeps 12 hours a day, and has increased appetite, poor concentration at work, and fleeting thoughts of suicide. The patient has no medical history and laboratory evaluation is unremarkable. Major depressive disorder is diagnosed and antidepressant medication administered. Several weeks after starting the medication, the patient's depressive symptoms are mildly improved, but he is now distressed by a significant decrease in libido and impaired sexual performance. He is considering stopping the medication and requests an alternate treatment. Which of the following drugs is most appropriate for this patient?

A. Bupropion
B. Citalopram
C. Imipramine
D. Sertraline
E. Trazodone
F. Venlafaxine

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- ✓ A. Bupropion (76%)
- B. Citalopram (1%)
- C. Imipramine (2%)
- D. Sertraline (4%)
- E. Trazodone (7%)
- F. Venlafaxine (7%)

Omitted
Correct answer
A

76%
Answered correctly

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Time Spent

01/27/2020
Last Updated

Explanation

This patient was most likely treated with a **selective serotonin reuptake inhibitor** (SSRI), a commonly prescribed initial treatment for major depressive disorder that causes **sexual dysfunction** in up to 50% of patients. SSRI-related sexual side effects include decreased libido, decreased arousal, anorgasmia, and increased ejaculation latency.

Bupropion is an antidepressant that **does not cause sexual dysfunction**. It is classified as a norepinephrine-dopamine reuptake inhibitor.

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Bupropion is an antidepressant that **does not cause sexual dysfunction**. It is classified as a norepinephrine-dopamine reuptake inhibitor. Because of its stimulating effects, bupropion is useful in treating depression associated with hypersomnia and low energy. Bupropion is also preferred because it causes less weight gain compared with other antidepressants.

Bupropion is contraindicated in patients with bulimia nervosa, anorexia nervosa, and seizure disorders because it lowers the seizure threshold.

(Choices B and D) Citalopram and sertraline are SSRIs that would likely cause sexual dysfunction in this patient. Switching to a non-SSRI such as bupropion is more likely to improve his sexual dysfunction.

(Choice C) Imipramine is a tricyclic antidepressant with numerous side effects, including sexual dysfunction. These types of antidepressants are dangerous in overdose because of cardiotoxicity, so they are not a first-line treatment for depression.

(Choice E) Trazodone is a highly sedating antidepressant that can be helpful for patients with insomnia. Trazodone can cause sexual dysfunction and priapism, a rare but serious side effect.

(Choice F) Venlafaxine is a serotonin-norepinephrine reuptake inhibitor that can cause sexual side effects.

Educational objective:
Sexual dysfunction is seen in up to 50% of patients treated with selective serotonin reuptake inhibitors. Bupropion, a norepinephrine-dopamine reuptake inhibitor, is a first-line treatment for major depressive disorder and does not cause sexual dysfunction.

References

- Bupropion in the depression-related sexual dysfunction: a systematic review.
- Bupropion.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Antidepressants
Subject	System	Topic

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A 27-year-old man with schizophrenia comes to the emergency department due to an acute muscle spasm in his neck that developed several days after starting treatment with haloperidol. He is extremely distressed and unable to turn his head. The patient is treated with intravenous diphenhydramine, which relieves his symptoms within minutes. A psychiatrist is consulted, and recommendations are made to discontinue haloperidol and start the second-generation antipsychotic quetiapine because of its lower risk for similar dystonic side effects. In addition to dopamine D2 receptor antagonism, this new medication has which of the following pharmacological properties?

A. Dopamine reuptake inhibition

B. Dopamine D2 partial agonist activity

C. Monoamine oxidase inhibition

D. Serotonin 2A receptor antagonism

E. Serotonin and norepinephrine reuptake inhibition

Submit

A 27-year-old man with schizophrenia comes to the emergency department due to an acute muscle spasm in his neck that developed several days after starting treatment with haloperidol. He is extremely distressed and unable to turn his head. The patient is treated with intravenous diphenhydramine, which relieves his symptoms within minutes. A psychiatrist is consulted, and recommendations are made to discontinue haloperidol and start the second-generation antipsychotic quetiapine because of its lower risk for similar dystonic side effects. In addition to dopamine D2 receptor antagonism, this new medication has which of the following pharmacological properties?

A. Dopamine reuptake inhibition (2%)

B. Dopamine D2 partial agonist activity (9%)

C. Monoamine oxidase inhibition (3%)

✓ D. Serotonin 2A receptor antagonism (70%)

E. Serotonin and norepinephrine reuptake inhibition (13%)

Omitted
Correct answer
D

70%
Answered correctly

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Explanation

	Primary mechanism of action	Key side effects
First-generation antipsychotics	• Potent dopamine D2 receptor antagonism	• Extrapyramidal symptoms (acute dystonia, akathisia, parkinsonism, tardive dyskinesia)

Explanation

	Primary mechanism of action	Key side effects
First-generation antipsychotics	• Potent dopamine D2 receptor antagonism	• Extrapyramidal symptoms (acute dystonia, akathisia, parkinsonism, tardive dyskinesia)
Second-generation antipsychotics	• Dopamine D2 receptor antagonism • Serotonin 2A receptor antagonism	• Metabolic syndrome, weight gain • Extrapyramidal symptoms (less common than FGAs)

FGAs = first-generation antipsychotics.

This patient developed an acute dystonic reaction (a type of extrapyramidal symptom [EPS]) several days after exposure to the **first-generation antipsychotic** (FGA) haloperidol. FGAs have a **high risk of causing EPS** due to their potent **dopamine D2 receptor antagonism**. Management of an acute dystonic reaction includes treatment with diphenhydramine or benztropine and switching to an agent with a lower propensity for producing EPS, such as a **second-generation antipsychotic** (SGA).

In addition to dopamine D2 receptor antagonism, SGAs (eg, olanzapine, quetiapine) **also block serotonin receptors**, specifically the 5-HT2A receptor. Compared with FGAs, SGAs block 5-HT2A receptors more potently than D2 receptors and have lower binding affinity at the dopamine receptor site, which is thought to explain the reduced risk of causing EPS. Although SGAs have a **low risk of EPS**, they are associated with a **greater risk** of **metabolic adverse effects**.

(Choice A) Dopamine reuptake inhibition, usually in combination with norepinephrine reuptake inhibition, is the mechanism of action of many drugs used to treat ADHD (eg, methylphenidate, bupropion).

(Choice B) Dopamine D2 partial agonism is one of the mechanisms of action of the SGAs aripiprazole and brexpiprazole.

(Choice C) The monoamine oxidase enzyme normally breaks down monoamines (eg, dopamine, norepinephrine, serotonin). The class of antidepressants known as monoamine oxidase inhibitors (eg, phenelzine, tranylcypromine) block these enzymes, thereby increasing availability of

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(Choice E) Serotonin and norepinephrine reuptake inhibition is the mechanism of action of serotonin and norepinephrine reuptake inhibitors (eg, venlafaxine) and tricyclic antidepressants (eg, amitriptyline).

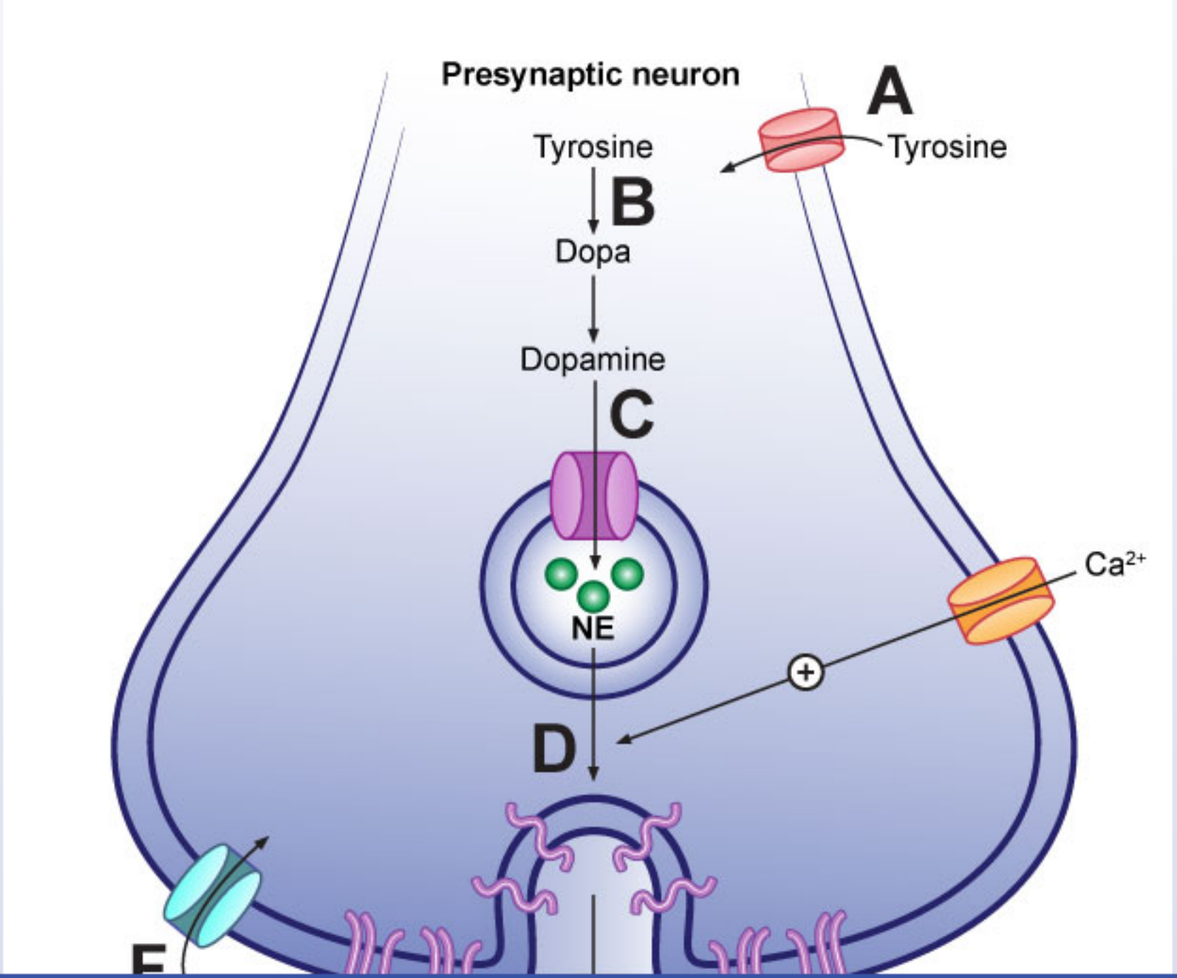
Educational objective:
Second-generation antipsychotics block 5-HT2A receptors and have lower binding affinity at dopamine D2 receptor sites, which is associated with a lower risk of extrapyramidal side effects.

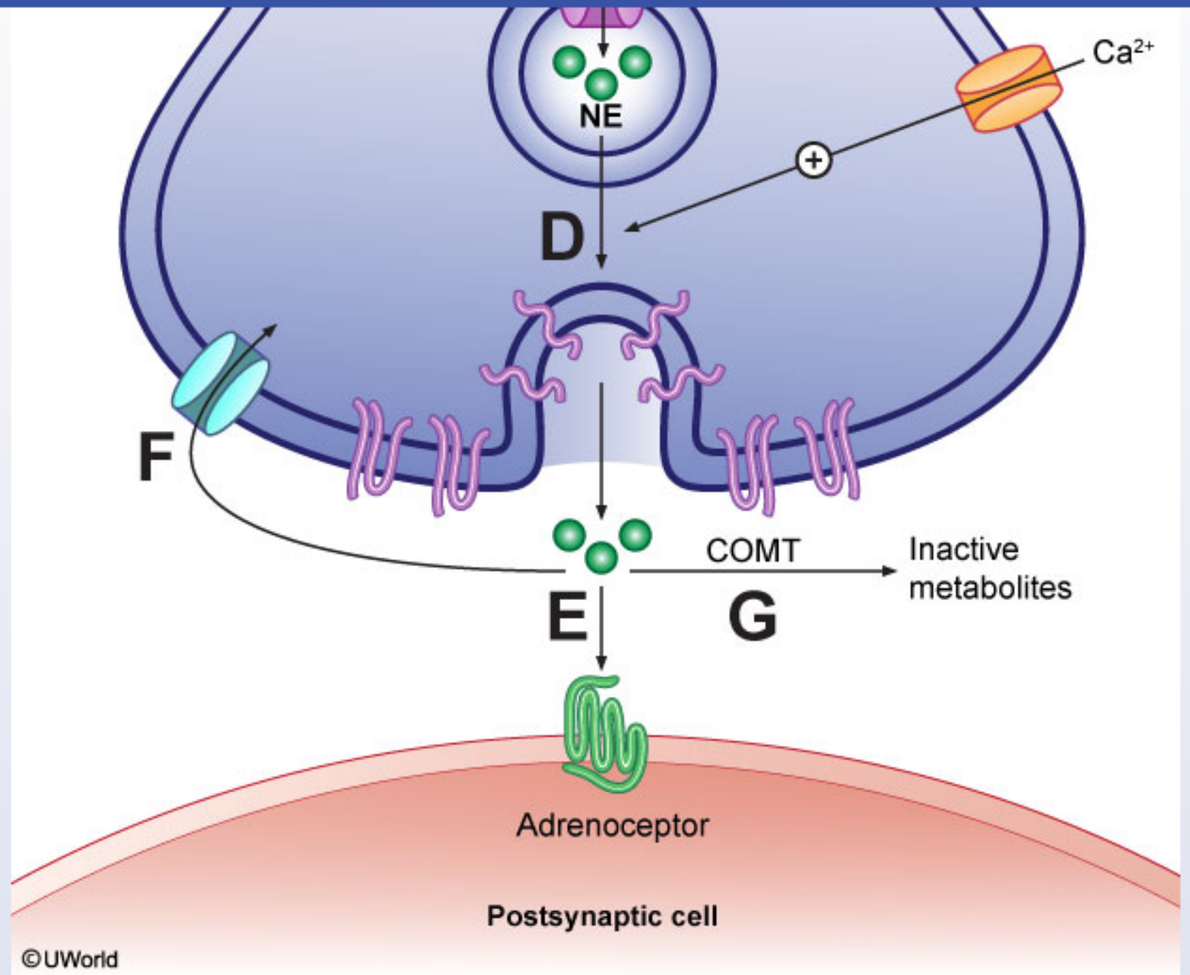
References

- Comparison of the anti-dopamine D2 and anti-serotonin 5-HT(2A) activities of chlorpromazine, bromperidol, haloperidol and second-generation antipsychotics parent compounds and metabolites thereof.
- Second-generation antipsychotics and extrapyramidal adverse effects.
- Safety, tolerability, and risks associated with first-and second-generation antipsychotics: a state-of-the-art clinical review.

Pharmacology Psychiatric/Behavioral & Substance Abuse Antipsychotics

A 32-year-old man is brought to the emergency department by police after an altercation at a local pub. He is agitated and says that his chest hurts. Blood pressure is 170/100 mm Hg and pulse is 130/min and regular. On physical examination, the patient is combative and uncooperative. There are no signs of physical injury. His pupils are dilated and reactive to light. Examination shows nasal perforation. ECG reveals myocardial ischemia. Inhibition of which of the following processes is most likely responsible for this patient's presentation?

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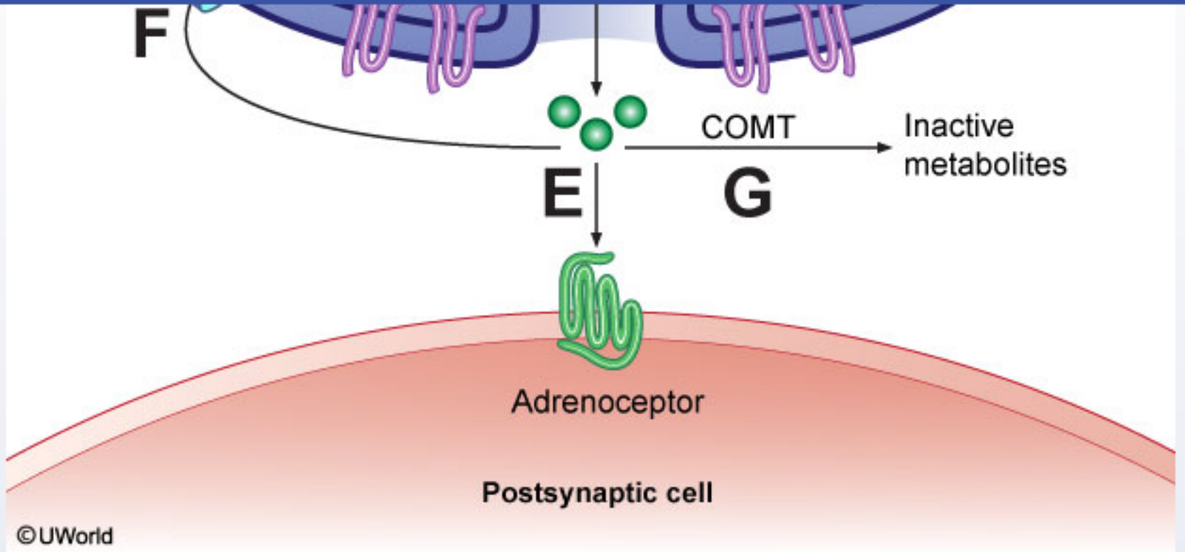

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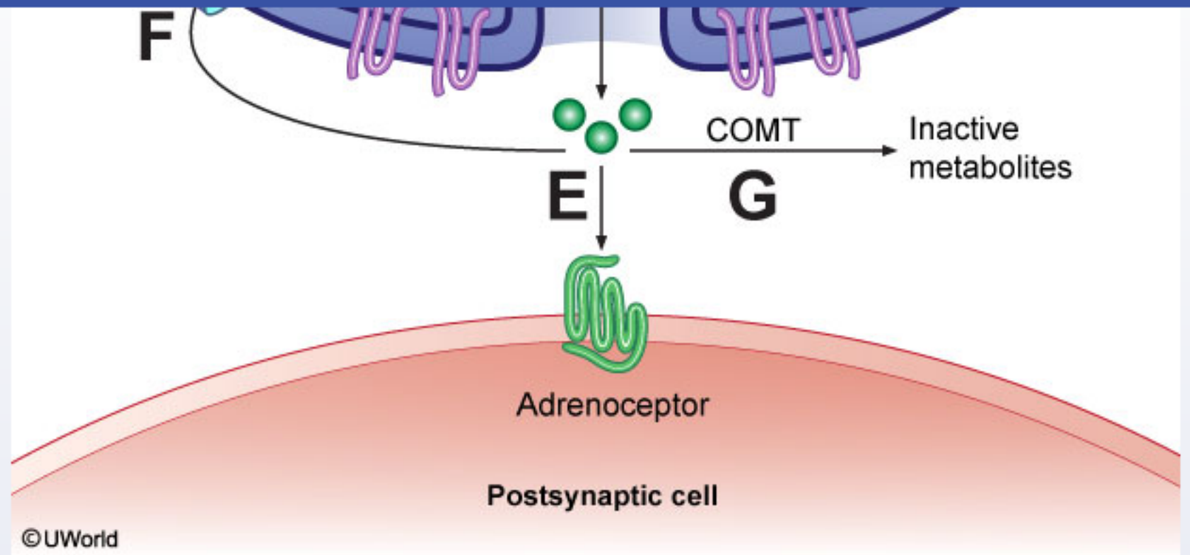

A. A (0%)
B. B (0%)
C. C (1%)
D. D (5%)
E. E (6%)
✓ F. F (75%)
G. G (9%)

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Correct answer

75%
Answered correctly

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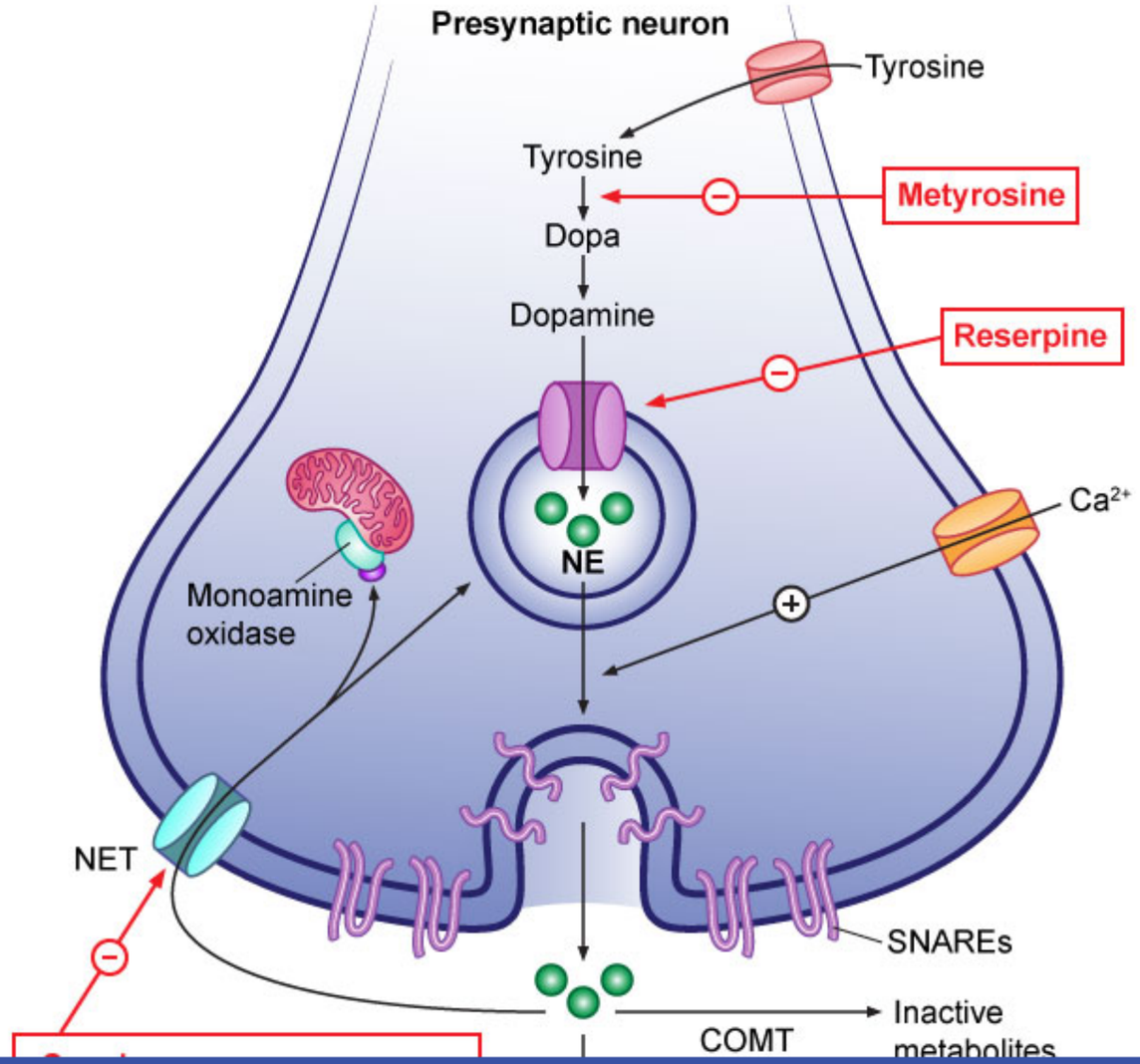
Blockers of catecholamine neurotransmitter release



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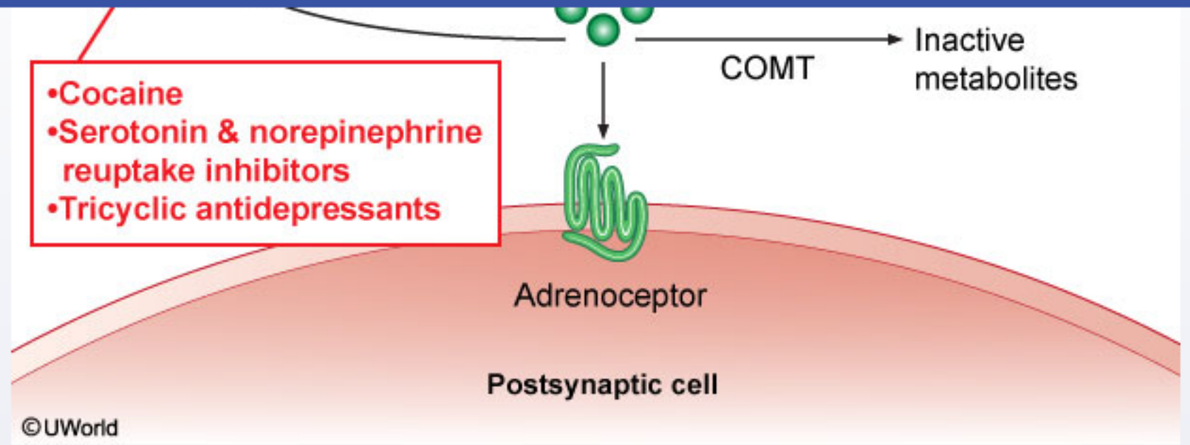

This patient is most likely acutely intoxicated with cocaine. Cocaine is a stimulant that inhibits presynaptic **reuptake of monoamines** (norepinephrine, dopamine, serotonin), resulting in **sympathetic stimulation** (eg, hypertension, tachycardia, light-responsive mydriasis) and CNS activation (eg, increased arousal, euphoria, agitation, seizures).

Cocaine's ability to increase synaptic availability of norepinephrine, combined with some of its other effects (eg, sodium channel antagonism), makes it a potent vasoconstrictor that can promote **myocardial ischemia** by causing **coronary artery vasospasm** and increased platelet aggregation (ie, thrombus formation). When cocaine is used intranasally, its vasoconstrictive effects cause local ischemia resulting in **mucosal atrophy** that can then lead to **nasal septal perforation**; these findings are highly suggestive of cocaine abuse.

(Choices A, D, and E) Inhibition of neuronal tyrosine uptake, impaired norepinephrine release into the synaptic cleft, or blockade of postsynaptic adrenergic receptors would result in sympatholytic effects (reduced blood pressure and heart rate).

(Choice B) Metyrosine blocks the rate-limiting step of catecholamine synthesis (tyrosine hydroxylase). This results in decreased levels of catecholamines and sympatholytic effects.

(Choice C) Reserpine (an antihypertensive agent no longer in clinical use) blocks monoamine entry into presynaptic vesicles, resulting in sympatholytic effects.

(Choice G) Catechol-O-methyl transferase (COMT) is found in the brain and liver and degrades catecholamine neurotransmitters. Entacapone and tolcapone are COMT inhibitors used to prolong the effects of levodopa treatment in patients with Parkinson disease.

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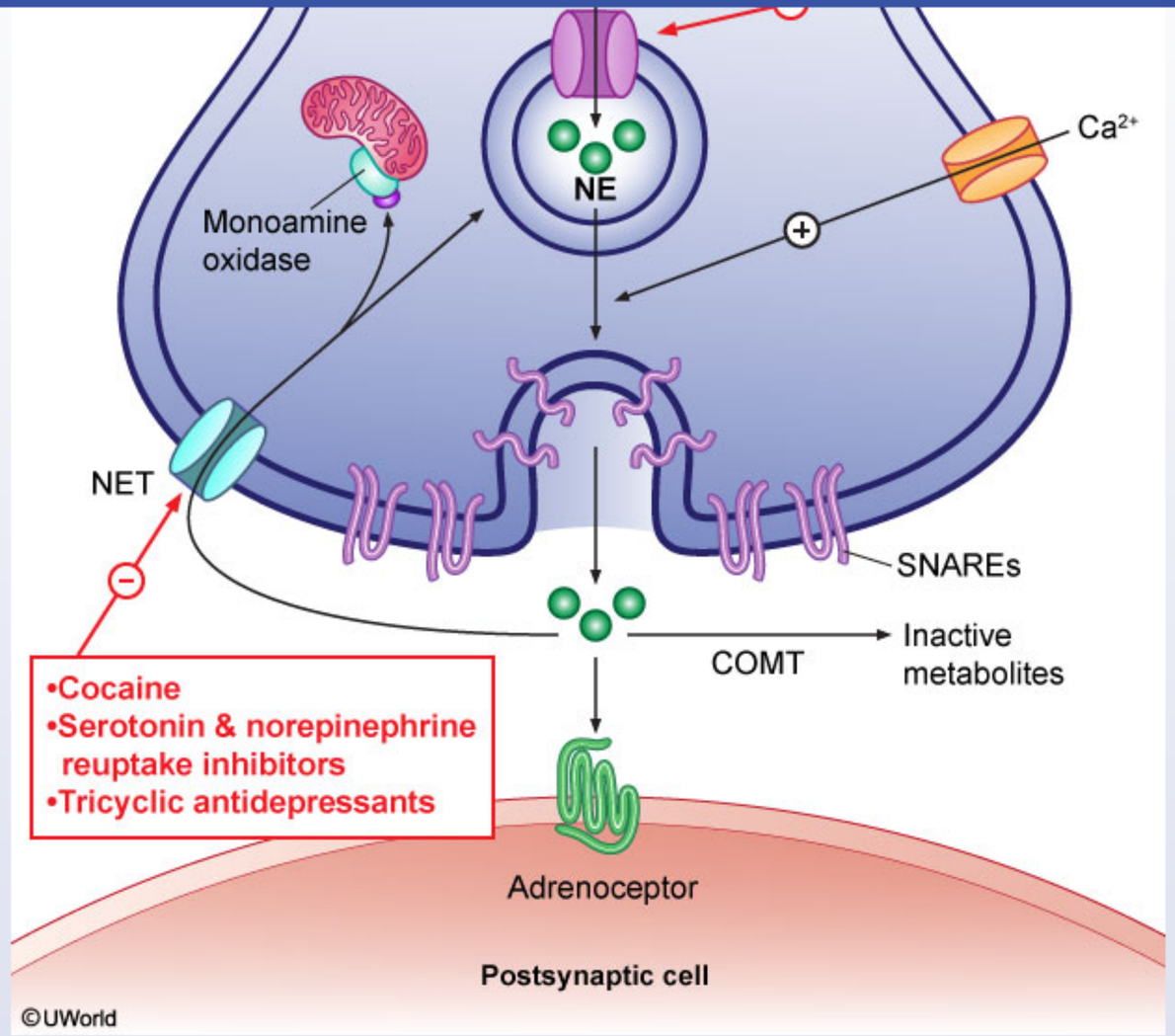

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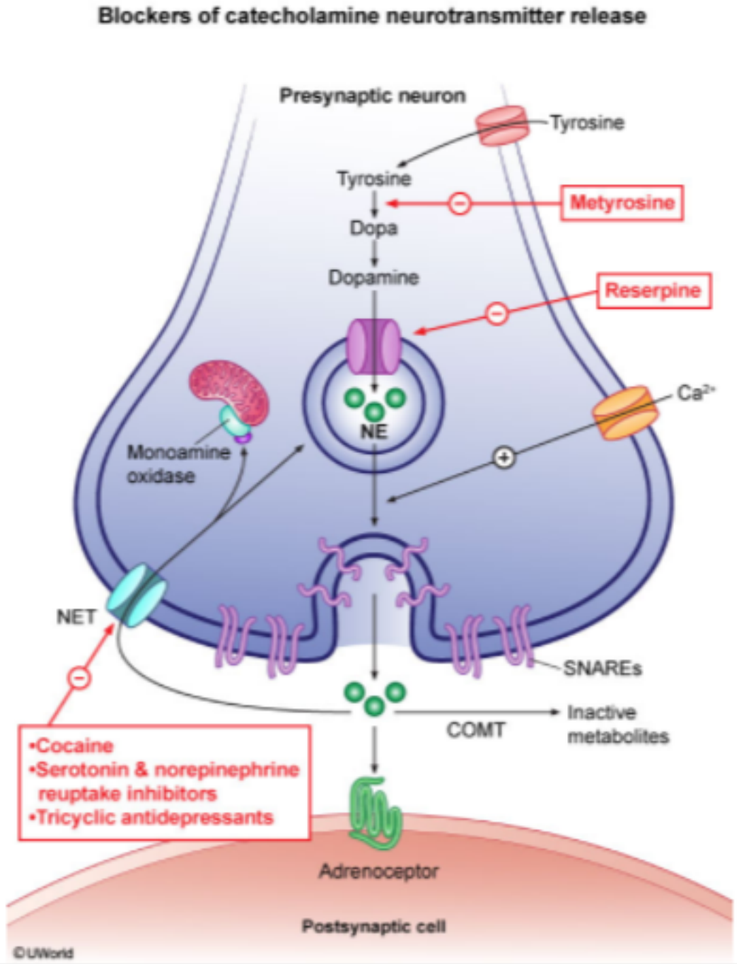

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This patient is most likely acutely intoxicated with cocaine. Cocaine is a stimulant that inhibits presynaptic **reuptake of monoamines** (norepinephrine, dopamine, serotonin), resulting in **sympathetic stimulation** (eg, hypertension, tachycardia, light-responsive mydriasis) and CNS activation (eg, increased arousal, euphoria, agitation, seizures).

Cocaine's ability to increase synaptic availability of norepinephrine, combined with some of its other effects (eg, sodium channel antagonism), makes it a potent vasoconstrictor that can promote **myocardial ischemia** by causing **coronary artery vasospasm** and increased platelet aggregation (ie, thrombus formation). When cocaine is used intranasally, its vasoconstrictive effects cause local ischemia resulting in **mucosal atrophy** that can then lead to **nasal septal perforation**; these findings are highly suggestive of cocaine abuse.

(Choices A, D, and E) Inhibition of neuronal tyrosine uptake, impaired norepinephrine release into the synaptic cleft, or blockade of postsynaptic adrenergic receptors would result in sympatholytic effects (reduced blood pressure and heart rate).

(Choice B) Metyrosine blocks the rate-limiting step of catecholamine synthesis (tyrosine hydroxylase). This results in decreased levels of catecholamines and sympatholytic effects.

(Choice C) Reserpine (an antihypertensive agent no longer in clinical use) blocks monoamine entry into presynaptic vesicles, resulting in sympatholytic effects.

(Choice G) Catechol-O-methyl transferase (COMT) is found in the brain and liver and degrades catecholamine neurotransmitters. Entacapone and tolcapone are COMT inhibitors used to prolong the effects of levodopa treatment in patients with Parkinson disease.

Educational objective:
Cocaine is a stimulant that inhibits the presynaptic reuptake of norepinephrine, dopamine, and serotonin. Intoxicated patients develop agitation, tachycardia, hypertension, and light-responsive mydriasis due to increased sympathetic activity. Cocaine is also a potent vasoconstrictor that can cause myocardial ischemia and atrophy of the nasal mucosa and septum.

References

- Cardiovascular consequences of cocaine use.
- Cocaine intoxication.

Pharmacology Psychiatric/Behavioral & Substance Abuse Cocaine

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A 38-year-old woman comes to the office due to breast tenderness and absence of menstrual periods over the last 3 months. The patient has a history of schizophrenia and familial hypercholesterolemia. Medications include risperidone, which has led to significant improvement in psychotic symptoms, and atorvastatin. BMI is 26 kg/m^2, down from 30 kg/m^2 6 months ago after following a strict dietary plan. Basic serum chemistry panel and thyroid function tests are normal, and urine pregnancy test is negative. Which of the following is the most likely explanation for this patient's amenorrhea?

A. 21-hydroxylase deficiency
B. Asherman syndrome
C. Drug-induced amenorrhea
D. Polycystic ovary syndrome
E. Primary ovarian insufficiency
F. Weight loss

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- A. 21-hydroxylase deficiency (0%)
- B. Asherman syndrome (0%)
- ✓ C. Drug-induced amenorrhea (81%)
- D. Polycystic ovary syndrome (1%)
- E. Primary ovarian insufficiency (1%)
- F. Weight loss (13%)

Omitted
Correct answer
C

81%
Answered correctly

02 secs
Time Spent

01/28/2020
Last Updated

Explanation

Prolactin

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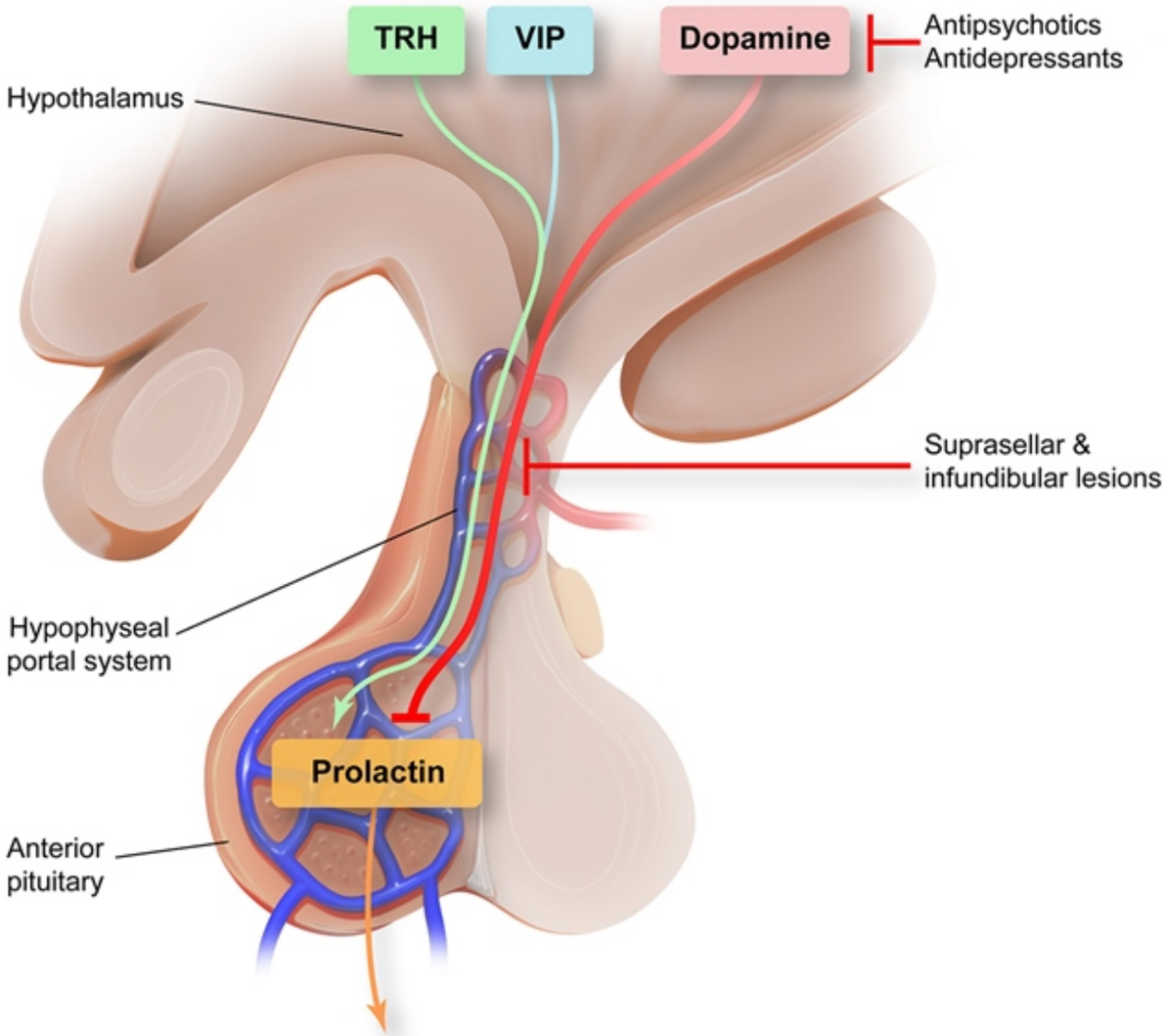
Prolactin



This patient with amenorrhea and breast tenderness likely has drug-induced hyperprolactinemia due to **risperidone**, an antipsychotic drug used in the management of schizophrenia. Its primary action is to **inhibit** dopamine **D2 receptors**, but it also has inhibitory effects on serotonergic and alpha-adrenergic pathways.

Secretion of prolactin from the anterior pituitary is primarily regulated by the inhibitory effect of hypothalamic dopamine; stimulation of D2 receptors on lactotrophs decreases the synthesis and release of prolactin. Because risperidone and other antipsychotic drugs block D2 receptor activation, there is a **loss of the normal tonic inhibition of prolactin release**, leading to **hyperprolactinemia** in some cases. This can result in galactorrhea and breast soreness. In addition, elevated prolactin levels inhibit release of gonadotropin-releasing hormone from the hypothalamus, resulting in central hypogonadism and **amenorrhea**.

(Choice A) Nonclassic 21-hydroxylase deficiency may be associated with menstrual irregularity (most often oligomenorrhea), hirsutism, and acne in women. Nonclassic 21-hydroxylase deficiency most often presents in childhood or adolescence.

(Choice B) Asherman syndrome refers to the presence of severe intrauterine adhesions that cause amenorrhea and infertility. It typically occurs in patients who have had multiple dilation and curettage procedures or those with chronic endometritis.

(Choice D) Polycystic ovary syndrome is characterized by infertility, oligomenorrhea, and hyperandrogenism. It typically begins in adolescence and is unlikely to develop in a 38-year-old woman. Most patients with polycystic ovary syndrome are obese. Insulin resistance is thought to play a central role in its pathogenesis.

(Choice E) Primary ovarian insufficiency is characterized by amenorrhea, hypoestrogenism, and elevated serum gonadotropin levels in women age <40. The decreased estrogenic effect on breast tissue can cause a decline in breast density but would not cause tenderness.

(Choice F) Severe weight loss (eg, anorexia nervosa), intense exercise, and/or severe stress can cause amenorrhea by inducing functional hypothalamic amenorrhea. However, none of these would cause breast tenderness.

Educational objective:
The secretion of prolactin is controlled by the inhibitory effect of hypothalamic dopamine. Risperidone and other antipsychotics cause hyperprolactinemia by blocking D2 receptors on lactotrophs. Elevated prolactin leads to amenorrhea (inhibition of gonadotropin-releasing hormone release), galactorrhea, and breast soreness.

References

(Choice A) Nonclassic 21-hydroxylase deficiency may be associated with menstrual irregularity (most often oligomenorrhea), hirsutism, and acne in women. Nonclassic 21-hydroxylase deficiency most often presents in childhood or adolescence.

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References

- Antipsychotic-induced hyperprolactinemia: synthesis of world-wide guidelines and integrated recommendations for assessment, management and future research.
- Clinical management of antipsychotic-induced hyperprolactinemia.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Antipsychotics
Subject	System	Topic

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A 7-year-old boy is brought to the emergency department by his older sister after being found in their mother's bathroom with an open bottle of pills. The bottle is unlabeled and the boy is unable to describe how many pills he ingested. The sister, who was babysitting, became alarmed when the boy subsequently became increasingly lethargic over the next hour. The mother takes medications for anxiety, depression, and chronic lower back pain. On arrival, the boy is somnolent and difficult to arouse. Temperature is 36.7 C (98 F), blood pressure is 100/60 mm Hg, pulse is 75/min, and respirations are 16/min. Physical examination is unremarkable. Which of the following drugs is most likely to reverse this patient's symptoms?

A. Cyproheptadine
B. Diphenhydramine
C. Flumazenil
D. Naloxone
E. Physostigmine

Submit

A 7-year-old boy is brought to the emergency department by his older sister after being found in their mother's bathroom with an open bottle of pills. The bottle is unlabeled and the boy is unable to describe how many pills he ingested. The sister, who was babysitting, became alarmed when the boy subsequently became increasingly lethargic over the next hour. The mother takes medications for anxiety, depression, and chronic lower back pain. On arrival, the boy is somnolent and difficult to arouse. Temperature is 36.7 C (98 F), blood pressure is 100/60 mm Hg, pulse is 75/min, and respirations are 16/min. Physical examination is unremarkable. Which of the following drugs is most likely to reverse this patient's symptoms?

- A. Cyproheptadine (8%)
- B. Diphenhydramine (4%)
- ✓ C. Flumazenil (64%)
- D. Naloxone (20%)
- E. Physostigmine (2%)

Omitted
Correct answer
C

64%
Answered correctly

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Time Spent

02/01/2020
Last Updated

Explanation

Common toxidromes & antidotes		
Drug class	Clinical features	Antidote
	• Agitated delirium with sympathetic hyperactivity	

Common toxidromes & antidotes		
Drug class	**Clinical features**	**Antidote**
Anticholinergic agents	• Agitated delirium with sympathetic hyperactivity • Mydriasis, dry skin/mucous membranes, urinary retention	• Physostigmine
Benzodiazepines (eg, lorazepam)	• Sedation with normal vital signs • Slurred speech, ataxia	• Flumazenil
Opioids (eg, oxycodone)	• Sedation with respiratory suppression • Miosis, decreased bowel sounds	• Naloxone
Serotonergic agents (eg, SSRIs/SNRIs, TCAs, MAOIs)	• Serotonin syndrome: altered mental status, mydriasis, sympathetic hyperactivity, hyperreflexia/clonus	• Cyproheptadine

MAOIs = monoamine oxidase inhibitors; **SNRIs** = serotonin-norepinephrine reuptake inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

The presence of sedation with normal vital signs for age and an unremarkable physical examination is most consistent with **benzodiazepine overdose**. Benzodiazepines are often used in the treatment of anxiety disorders and alcohol withdrawal, as well as for procedural sedation. They bind as agonists at the benzodiazepine site on the $GABA_A$ receptor to potentiate the inhibitory effects of GABA, the major inhibitory neurotransmitter of the central nervous system. **Flumazenil** functions as a competitive **antagonist** at the **benzodiazepine binding site** and may be used as an antidote to reverse benzodiazepine sedation related to overdose or procedural sedation.

(Choice A) Cyproheptadine is a serotonin antagonist that has been used to treat severe cases of serotonin syndrome. Serotonin syndrome is characterized by altered mental status, autonomic hyperactivity (eg, tachycardia, hypertension), and hyperreflexia/myoclonus.

(Choice B) Diphenhydramine is an antihistamine that has been used to treat allergies and insomnia and to reverse antipsychotic drug–induced dystonic reactions.

(Choice D) Naloxone is an opioid antagonist that is indicated in patients with suspected opioid overdose (eg, decreased respiratory rate, miosis)

tricyclic antidepressants.

The presence of sedation with normal vital signs for age and an unremarkable physical examination is most consistent with **benzodiazepine overdose**. Benzodiazepines are often used in the treatment of anxiety disorders and alcohol withdrawal, as well as for procedural sedation. They bind as agonists at the benzodiazepine site on the $GABA_A$ receptor to potentiate the inhibitory effects of GABA, the major inhibitory neurotransmitter of the central nervous system. **Flumazenil** functions as a competitive **antagonist** at the **benzodiazepine binding site** and may be used as an antidote to reverse benzodiazepine sedation related to overdose or procedural sedation.

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(Choice B) Diphenhydramine is an antihistamine that has been used to treat allergies and insomnia and to reverse antipsychotic drug–induced dystonic reactions.

(Choice D) Naloxone is an opioid antagonist that is indicated in patients with suspected opioid overdose (eg, decreased respiratory rate, miosis). Opioid overdose is unlikely in this patient with age-appropriate normal vital signs.

(Choice E) Physostigmine is an acetylcholinesterase inhibitor that has been used as an antidote in severe cases of anticholinergic toxicity (dry mouth, mydriasis, tachycardia).

Educational objective:
Flumazenil is a benzodiazepine receptor antagonist. It can reverse the sedative effects of benzodiazepines related to overdose and procedural sedation.

References

- Flumazenil, naloxone and the 'coma cocktail.'

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Benzodiazepines
Subject	System	Topic

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A 34-year-old man is brought to the emergency department by his wife after she found him running around the yard in his underwear shouting, "I am going to change the world." She reports that he has a lot of energy despite hardly sleeping for the past 7 days, and that he recently quit his job to write a 500-page novel that he says "explains everything about the universe." The patient's history is significant for epilepsy with generalized seizures since childhood and a psychiatric hospitalization a year ago for a major depressive episode. Family history is significant for alcoholism and hypertension in his father and schizophrenia in his grandmother. Which of the following medications would be most helpful for long-term treatment of this patient's psychiatric condition as well as his seizure disorder?

A. Aripiprazole
B. Citalopram
C. Levetiracetam
D. Lithium
E. Lorazepam
F. Phenytoin
G. Valproate

Submit

A 34-year-old man is brought to the emergency department by his wife after she found him running around the yard in his underwear shouting, "I am going to change the world." She reports that he has a lot of energy despite hardly sleeping for the past 7 days, and that he recently quit his job to write a 500-page novel that he says "explains everything about the universe." The patient's history is significant for epilepsy with generalized seizures since childhood and a psychiatric hospitalization a year ago for a major depressive episode. Family history is significant for alcoholism and hypertension in his father and schizophrenia in his grandmother. Which of the following medications would be most helpful for long-term treatment of this patient's psychiatric condition as well as his seizure disorder?

- A. Aripiprazole (2%)
- B. Citalopram (1%)
- C. Levetiracetam (3%)
- D. Lithium (14%)
- E. Lorazepam (2%)
- F. Phenytoin (2%)
- ✓ G. Valproate (72%)

Omitted
Correct answer
G

72%
Answered correctly

02 secs
Time Spent

01/29/2020
Last Updated

Explanation

Mood stabilizers in bipolar disorder

Mood stabilizers in bipolar disorder		
	Indications	**Adverse effects**
Lithium	• Manic & depressive features	• Diabetes insipidus • Hypothyroidism • Tremor • Ebstein anomaly (teratogenic)
Valproate	• Manic features	• Hepatotoxicity • Neural tube defects (teratogenic)
Carbamazepine	• Manic features	• Aplastic anemia • SIADH • Neural tube defects (teratogenic)
Lamotrigine	• Depressive features	• Benign rash • Stevens-Johnson syndrome

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

This patient's history of major depression along with his current manic symptoms (ie, decreased need for sleep, grandiosity, goal-directed activity) indicate a diagnosis of bipolar disorder. **Valproate** (valproic acid) is used as an **anticonvulsant** and **mood stabilizer**. It blocks voltage-gated sodium channels and enhances the availability of GABA. As a mood stabilizer, it is used in acute mania and maintenance treatment of **bipolar disorder**. As an anticonvulsant, it effectively treats absence, myoclonic, and **generalized tonic-clonic seizures**. It is the drug of choice for **myoclonic seizures** and a second-line agent for absence seizures (for which ethosuximide is preferred).

Other anticonvulsants used as mood stabilizers in bipolar disorder include carbamazepine and lamotrigine. Carbamazepine is a CYP450 inducer that can cause lower levels of concomitant medications. Lamotrigine is associated with skin rash, which rarely can progress to life-threatening mucocutaneous reactions (eg, Stevens-Johnson syndrome).

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

This patient's history of major depression along with his current manic symptoms (ie, decreased need for sleep, grandiosity, goal-directed activity) indicate a diagnosis of bipolar disorder. **Valproate** (valproic acid) is used as an **anticonvulsant** and **mood stabilizer**. It blocks voltage-gated sodium channels and enhances the availability of GABA. As a mood stabilizer, it is used in acute mania and maintenance treatment of **bipolar disorder**. As an anticonvulsant, it effectively treats absence, myoclonic, and **generalized tonic-clonic seizures**. It is the drug of choice for **myoclonic seizures** and a second-line agent for absence seizures (for which ethosuximide is preferred).

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(Choice A) Aripiprazole is a second-generation antipsychotic used to treat psychotic and mood disorders. Antipsychotics are not indicated for seizures and may lower the seizure threshold.

(Choice B) Citalopram is a selective serotonin reuptake inhibitor (SSRI) antidepressant. SSRI monotherapy is avoided in bipolar disorder due to the risk of inducing mania. SSRIs have no role in the treatment of seizures.

(Choices C and F) Levetiracetam and phenytoin are anticonvulsants used in the treatment of epilepsy but they are not useful for treating bipolar disorder.

(Choice D) Lithium is a mood stabilizer that is effective for the treatment of bipolar disorder. Lithium is thought to modify second messenger signal transduction (eg, adenylyl cyclase and phospho-inositol pathways) at several levels, resulting in decreased excitatory neurotransmission. Lithium is not an anticonvulsant.

(Choice E) Lorazepam is a benzodiazepine that enhances the affinity of GABA for its receptor (increases frequency of chloride channel openings), thereby increasing its inhibitory potential. Lorazepam is a first-line medication for the treatment of active seizures, acute anxiety, and alcohol withdrawal.

Educational objective:
Lithium and the anticonvulsants valproate, carbamazepine, and lamotrigine are mood-stabilizing agents used in bipolar disorder. Valproate is commonly used in the treatment of generalized as well as myoclonic seizures.

mucocutaneous reactions (eg, Stevens-Johnson syndrome).

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References

- Anticonvulsants in bipolar disorders: current research and practice and future directions.
- Management of adverse effects of mood stabilizers.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Bipolar disorder
Subject	System	Topic

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A 65-year-old man is brought to the emergency department with new-onset confusion, suprapubic discomfort, and lack of urine output. His past medical history is significant for benign prostatic hyperplasia, hypertension, hyperlipidemia, and type 2 diabetes mellitus complicated by neuropathy. The patient also has a history of chronic insomnia and has been treated with several medications with little benefit. He does not know his current medications. On examination, the patient is afebrile, confused, and oriented only to self. Suprapubic fullness is present, but abdominal examination is otherwise unremarkable. A urinary catheter is placed and immediately drains 1000 mL of urine. Which of the following medications most likely has contributed to this patient's current condition?

A. Amitriptyline
B. Atorvastatin
C. Duloxetine
D. Finasteride
E. Gabapentin
F. Metformin
G. Tamsulosin

Submit

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- ✓ A. Amitriptyline (57%)
- B. Atorvastatin (1%)
- C. Duloxetine (8%)
- D. Finasteride (6%)
- E. Gabapentin (10%)
- F. Metformin (2%)
- G. Tamsulosin (14%)

Omitted
Correct answer
A

57%
Answered correctly

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Time Spent

01/20/2020
Last Updated

Explanation

Triguelis action	Corresponding side effects

Tricyclic action	Corresponding side effects
Inhibition of presynaptic **neurotransmitter reuptake** (norepinephrine & serotonin)	• Tremor • Insomnia
Blockade of cardiac **fast sodium channels**	• Conduction defects • Arrhythmias • **Hypotension**
Antagonism of central & peripheral **muscarinic acetylcholine receptors**	• **Confusion** • Dry mouth • **Constipation**, intestinal ileus • Hyperthermia, flushing • **Urinary retention**
Antagonism of peripheral **alpha-1 adrenergic receptors**	• **Orthostatic hypotension**, falls
Antagonism of **histamine (H1) receptors**	• **Sedation**

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Tricyclic antidepressants (TCAs), such as amitriptyline, are occasionally used for insomnia or adjunctive pain management when other medications are not effective. However, TCAs have strong **anticholinergic** properties that can lead to significant adverse effects such as **confusion**, constipation, and acute **urinary retention**. Elderly patients are at increased risk for side effects due to comorbid conditions (eg, dementia, benign prostatic hyperplasia), decreased hepatic and renal clearance of medications, and a higher burden of concurrent medications

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(Choices B and F) Metformin can cause lactic acidosis, and atorvastatin can cause hepatitis and myositis. These drugs do not have significant anticholinergic side effects.

(Choice C) Duloxetine is a dual serotonin and norepinephrine reuptake inhibitor used for the treatment of depression, anxiety, and a variety of chronic pain disorders. Duloxetine can cause confusion, but only rarely causes obstructive voiding symptoms.

(Choices D and G) Finasteride and tamsulosin are used for treatment of benign prostatic hyperplasia and should not cause urinary obstruction or retention.

(Choice E) Gabapentin is useful for painful diabetic neuropathy. It can cause sedation, confusion, and incoordination, but it does not have significant anticholinergic side effects.

Educational objective:
Tricyclic antidepressants have strong anticholinergic properties. Potential side effects include confusion, constipation, and urinary retention. These medications should be used with caution in elderly patients.

References

- Effects of treatments for symptoms of painful diabetic neuropathy: systematic review.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Urinary retention
Subject	System	Topic

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Pharmacology	Psychiatric/Behavioral & Substance Abuse	Urinary retention
Subject	System	Topic

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A 22-year-old college student seeks treatment for depressed mood, low energy, poor concentration, and feelings of worthlessness and guilt following a breakup with her partner of 2 years. She is diagnosed with major depression and treated with bupropion and psychotherapy. After 3 weeks of treatment, the patient reports that her energy and motivation have improved somewhat. Her grades, which had been deteriorating, have stabilized. The patient is also continuing to receive psychotherapy and believes that it is beneficial. However, she still feels "really down" at times and has a poor appetite. Further history suggests that the patient consumes very little food each day (a pattern that preceded her use of bupropion) and exercises excessively. Due to her ongoing mood problems, increasing the dose of her antidepressant medication is considered. Which of the following potential side effects of the increased dose would be of primary concern?

A. Agranulocytosis
B. Hypertension
C. Seizures
D. Sexual dysfunction
E. Stevens-Johnson syndrome
F. Weight gain

Submit

A 22-year-old college student seeks treatment for depressed mood, low energy, poor concentration, and feelings of worthlessness and guilt following a breakup with her partner of 2 years. She is diagnosed with major depression and treated with bupropion and psychotherapy. After 3 weeks of treatment, the patient reports that her energy and motivation have improved somewhat. Her grades, which had been deteriorating, have stabilized. The patient is also continuing to receive psychotherapy and believes that it is beneficial. However, she still feels "really down" at times and has a poor appetite. Further history suggests that the patient consumes very little food each day (a pattern that preceded her use of bupropion) and exercises excessively. Due to her ongoing mood problems, increasing the dose of her antidepressant medication is considered. Which of the following potential side effects of the increased dose would be of primary concern?

- A. Agranulocytosis (2%)
- B. Hypertension (4%)
- ✓ C. Seizures (75%)
- D. Sexual dysfunction (6%)
- E. Stevens-Johnson syndrome (1%)
- F. Weight gain (8%)

Omitted
Correct answer
C

75%
Answered correctly

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01/27/2020
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Explanation

Bupropion is an antidepressant that works by inhibiting the reuptake of norepinephrine and dopamine. It is commonly used to treat major depression and is often preferred by patients because it does not cause weight gain or sexual side effects.

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Seizures are a potential side effect of bupropion therapy, especially when the medication is given at high doses. The risk is even greater in patients with pre-existing seizure disorders or eating disorders with potential electrolyte imbalances. Bupropion is therefore **contraindicated** in patients with **seizure disorders** or current or prior diagnosis of **bulimia** or **anorexia nervosa**. This patient's possible food restriction and excessive exercise suggest the possibility of an eating disorder, and the increased seizure risk with a higher dosage of bupropion would be of primary concern.

(Choice A) Agranulocytosis is a side effect related to treatment with the antipsychotic clozapine. The mood-stabilizing agents carbamazepine and valproate can also be associated with bone marrow abnormalities.

(Choice B) Bupropion has minimal effects on blood pressure. The serotonin-norepinephrine reuptake inhibitor venlafaxine has been associated with increased blood pressure, especially at higher doses.

(Choice D) Sexual dysfunction is a relatively common side effect of selective serotonin reuptake inhibitors (SSRIs), which limits their use for many patients. Bupropion has no effect on serotonin and does not cause sexual dysfunction. It can be used as an adjunct to treat SSRI-related sexual dysfunction.

(Choice E) Rash, including life-threatening Stevens-Johnson syndrome, rarely occurs with bupropion. It is more commonly seen with the anticonvulsant lamotrigine, which is used to treat bipolar depression.

(Choice F) Bupropion is either weight neutral or associated with mild weight loss.

Educational objective:
Bupropion is a first-line antidepressant that is not associated with sexual side effects or weight gain. However, it is associated with an increased seizure risk at high doses and is contraindicated in patients with seizure disorders, anorexia nervosa, and bulimia.

References

- Seizure secondary to bupropion extended release preparation: a report.
- Epileptic seizures, coma and EEG burst-suppression from suicidal bupropion intoxication.

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A 40-year-old woman is brought to the emergency department due to ataxia and tremor. The patient's symptoms started gradually 2 weeks ago and have worsened acutely over the past 2 days. She is having difficulty walking and almost fell while getting up from a chair. The patient's medical problems include bipolar disorder and recently diagnosed hypertension. Her medications include a stable dose of lithium for many years and a new blood pressure medication that was started several weeks ago. Vital signs are within normal limits. Neurologic examination reveals a resting tremor and difficulty with balance. Physical examination is otherwise normal. A drug interaction involving which of the following medications is most likely causing this patient's condition?

A. Amiloride
B. Clonidine
C. Hydralazine
D. Hydrochlorothiazide
E. Metoprolol

Submit

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A. Amiloride (9%)
B. Clonidine (11%)
C. Hydralazine (6%)
✓ D. Hydrochlorothiazide (68%)
E. Metoprolol (4%)

Omitted
Correct answer
D

68%
Answered correctly

02 secs
Time Spent

02/02/2020
Last Updated

Explanation

Lithium toxicity	
	Acute toxicity • Intentional overdose

Lithium toxicity	

Etiology	Acute toxicity
	• Intentional overdose
	Chronic toxicity
	• Decreased renal perfusion (↓ lithium clearance)
	  ◦ Dehydration
	  ◦ Thiazide diuretics, NSAIDs, ACE inhibitors

Clinical features	Acute toxicity • **Gastrointestinal**: nausea, vomiting, diarrhea • Late neurologic sequelae Chronic toxicity **(neurologic)** • Lethargy, confusion, agitation • Ataxia, tremor/fasciculations, seizure
Treatment	• Intravenous hydration • Hemodialysis (severe cases)

NSAID = nonsteroidal anti-inflammatory drug.

Lithium has a very **narrow therapeutic index**. Patients with acute toxicity initially develop symptoms of gastrointestinal upset (eg, vomiting, diarrhea) with later development of neurologic findings (eg, neuromuscular excitability, delirium) as the drug penetrates the central nervous system. However, **chronic lithium toxicity** generally presents with **gradual onset of neurologic symptoms**, such as this patient's worsening **ataxia** and **tremor**.

Lithium is similar to sodium in its properties and is almost exclusively excreted by the kidneys. Like sodium, it is filtered and reabsorbed mostly in the proximal tubules (>60%). Any cause of decreased glomerular filtration (eg, volume depletion, congestive heart failure, cirrhosis) can increase proximal sodium/lithium reabsorption and lead to increased lithium retention.

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Thiazide diuretics limit sodium reabsorption in the distal tubule, causing mild volume depletion (and potential hyponatremia) that stimulates proximal tubular sodium/lithium reabsorption, leading to lithium toxicity over time. ACE inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) can also impair lithium clearance and lead to toxicity.

(Choice A) Amiloride is a potassium-sparing diuretic that works primarily on the distal tubule and collecting duct by inhibiting sodium reabsorption. Potassium-sparing diuretics often decrease serum lithium levels.

(Choices B, C, and E) Clonidine, hydralazine, and metoprolol do not alter renal ion exchange or cause volume depletion and therefore do not cause lithium toxicity.

Educational objective:
Chronic lithium toxicity (eg, confusion, ataxia, neuromuscular excitability) can be precipitated by volume depletion and drug interactions with thiazide diuretics, ACE inhibitors, and nonsteroidal anti-inflammatory drugs.

References

- Drug interactions with lithium: an update.

Pharmacology	Psychiatric/Behavioral & Substance Abuse	Lithium
Subject	System	Topic

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